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ORIGINAL ARTICLES

FILARIASIS IN SOLDIERS ON AN ISLAND IN THE SOUTH PACIFIC

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Filariasis has been known to exist on the islands of the eastern part of the South Pacific Ocean for many years. Several investigations have been carried out among the natives of these islands, as a result of which the infection is attributed to *Wuchereria bancrofti*. The life cycle of the parasite and its transmission by the mosquito are well known and will not be described in this article.

The Authors were attached to a small field hospital accompanying a task force. The personnel included no one specially trained in tropical medicine. For some months the outfit was incompletely equipped to study or to attempt the control of the disease to be described. From the information supplied by medical officers who had arrived in this area earlier, and from observations among the natives, which are described later, we soon became aware of the possibility that filariasis might appear among the troops under our care. A study of the literature available to us gave no clue as to the manner in which soldiers freshly infected would react to the disease. No information could be obtained as to how soon after the first exposure to the infection symptoms or signs should be expected.

The purpose of this article is to describe the clinical picture presented in the course of time by soldiers among the troops on the island. The account which is given here is specifically based on the study of 127 soldier patients. We believe, in common with many other medical officers with a similar experience, that this is the picture of early filariasis and that our observations furnish a basis for the clinical diagnosis of early filariasis, as will be described later. Seldom, if ever, has such an opportunity for the study of the beginning of this disease in freshly exposed adults previously offered itself. The opportunity also existed for comparison with a large group of natives who had had filariasis all their lives. A short account of the disease among natives, therefore, is included in the latter part of the article.

Incubation Period. A conclusive statement of the length of the incubation period cannot be made. The shortest time after first exposure in which any of our patients developed symptoms which were definitely attributed to filariasis was 3 months. Mild symptoms appeared in the majority of cases after 5 months' exposure, while more severe symptoms were seen, as a rule, after 8 months. In some cases, 14 months elapsed before the development of symptoms. It seems likely that the incubation period varies a good deal in length.

Symptoms and Signs. When the records of patients who developed characteristic signs were examined, it was found that most of these patients had complained of undiagnosable symptoms beforehand. In retrospect, it became apparent that many soldiers had reported to the dispensary with these early symptoms for some time before the possibility that they might be associated with filariasis was recognized. Common among these symptoms were anorexia, nausea and vomiting, and pains having a variable and remarkable distribution to the back, suprapubic region, groin, spermatic cord, testicles, and the inside of the thighs. The severity of these symptoms varied greatly, often being mild, but occasionally requiring hospitalization. Pain in the scrotum was sometimes described as being as great as if the patient had been kicked. In general, the more severe the early symptoms, the more marked were the later manifestations.

Further developments were found to occur, as a rule, from 10 to 14 days after the first symptoms. They consisted for the most part of involvement of the scrotal contents which occurred in 75% of our patients and of involvement of superficial lymph vessels and nodes of the arm or leg.

The first physical finding was often acute epididymitis with swelling and tenderness of the upper pole, which in time affected the whole organ. The most frequent abnormality was acute funiculitis. It was observed in some cases that epididymitis subsided when funiculitis developed; in other instances the two lesions coëxisted. There was usually marked tenderness over the inguinal canal, especially over the internal ring. Sometimes the swollen cord could be felt in the canal. Swelling of the cord where it emerges from the external ring was detectable early in the course. In size the swollen cord varied from 2 to 5 times its normal diameter. Varicoceles, usually lasting only a week or two, developed in some patients with funiculitis. In some instances there was an exacerbation of a chronic varicocele. No diagnostic weight was given to this particular development, because of its frequent occurrence in other circumstances. Tense swelling of the testicle to twice its usual size was a common finding. Hydrocele was not encountered in soldier patients, although it was found in many natives with late disease. Generalized scrotal swelling, with soft, boggy thickening of the wall appeared only after some weeks, usually in association with changes in the scrotal contents.

It was observed that pain often disappeared when the scrotal swelling became maximal. Many patients with these lesions suffered from severe malaise, cold sweats, nervousness and worry. Since all patients

had seen numerous cases of advanced elephantiasis among natives, the source of such nervousness was obvious.

Involvement of the superficial lymph nodes and vessels was much less frequent than that of the scrotal contents. When it occurred in these patients, it was associated with pain, tenderness, and swelling. In the arm, the axillary nodes were first affected, later the epitrochlear. A wide red streak which was raised, extremely tender, and could be felt as a cordlike structure, extended along the inner border from the axilla to the elbow. It was often over ½ inch in width. In some cases cellulitis developed, especially below the biceps muscle, which tended to become a burrowing abscess. Occasionally the lymphangitis proceeded down both sides of the forearm, even into the fingers which become swollen and painful. The same chain of events was observed in the thigh, beginning with the nodes of the groin and spreading down the medial side, but seldom going below the knee. In a few cases, however, the only finding was lymphangitis of the ankle and foot. In these instances, it seems probable that deep lymphatics higher up were involved. When cellulitis occurred in the thigh, it was usually confined to the upper inner third. Patients often complained strongly of pain on walking. The progress of lymphangitis was frequently observed and was always noted to proceed toward the periphery, both in the arm and in the leg.

The most important of these findings are listed in Table 1. They were seen in many different combinations. As the table indicates, for unknown reasons, involvement of the scrotal contents on the left side was much more frequent than on the right. The left arm and leg were more often affected than the right, but the number of cases here was small.

TABLE 1.—THE OCCURRENCE OF CERTAIN LESIONS IN 127 PATIENTS

Lesion	No. of patients		
	Left	Right	Total
Funiculitis	95	32	127
Orchitis	48	21	69
Epididymitis	11	11	22
Lymphadenitis, acute	9	..	9
Lymphangitis, acute	8	..	8
Cellulitis, acute	9	..	9

Abscesses considered to be associated with filariasis developed in 2 soldiers, following cellulitis of the elbow region. On incision, these abscesses were deep and had many pockets which had to be broken up in order to effect complete drainage. The pus obtained was thin, greenish in color, and showed no organisms on direct microscopic examination. These lesions closely resembled the abscesses described below, which were observed among natives.

A quite different type of swelling occurred in some of our patients. This was a soft, non-suppurative swelling with no sign of acute inflammation, affecting an area 3 to 6 inches in diameter on the arm, hand, or leg. In a few instances more than one of these swellings was found at the same time in the same individual. Some 6 patients developed

similar swellings of the upper eyelid. A number of men had urticaria at the time swellings of this type were present. All of these swellings were transient. As a result of our experience, we came to consider the multiple occurrence and transiency of these peculiar lesions as important diagnostic findings.

Fever was only observed in significant degree when acute cellulitis or lymphangitis was present.

Blood Counts. As has been previously stated, our laboratory facilities were simple and elaborate examinations were out of the question. Red blood cell counts showed no significant anemia. White blood cell counts showed a moderate increase when cellulitis or lymphangitis and fever were present, but were otherwise within normal limits. In early cases the differential white cell count was usually normal. After 2 or 3 weeks' illness, however, the eosinophils were often increased. Among 127 patients, 56 (44%) showed more than 4% eosinophils, the maximum count being 44% (Table 2). Thick blood smears were studied with great care in 100 of our Army patients and failed to show any suggestion of a microfilaria.

Material to use in the performance of skin tests was not available.

TABLE 2.—PERCENTAGE OF EOSINOPHIL CELLS FOUND IN 127 PATIENTS

Eosinophils (%)	No. of patients
1 to 2	35
4	36
6 to 9	39
10 to 19	12
20 to 29	4
44	1

The Course of the Disease. Since the clinical findings and course comprise one of the most important approaches to the problem under discussion, it seems desirable to recapitulate these aspects of the disease. Patients first presented themselves from 3 to 14 months after first arrival in this area. The earliest symptoms, malaise, insomnia, anorexia, nausea, vomiting, and pain in various parts of the body, were not suggestive of any specific diagnosis. After an interval of about 2 weeks, pain, tenderness, and swelling appeared in the scrotal contents and spermatic cord as described above. Some of the patients developed the signs of acute lymphadenitis and lymphangitis, usually of the upper arm and thigh. Severe pain, marked swelling and acute lymphangitis required hospitalization, but usually subsided in a week or two. However, symptoms and signs usually persisted in some degree for several weeks, during which the patients were ambulatory. During this period, there was much variation from day to day in the severity of the disease. Both symptoms and swellings were aggravated by exertion and on hot, humid days; rest and cool weather had the opposite effect. In most cases an interval of freedom from trouble followed. Recurrences appeared, however, in the patients that remained under observation, after 1 to 3 months. As seen on the island, recurrent attacks appeared to be increasingly severe and persistent. Observations were cut short by the evacuation of patients.

Epidemiologic Considerations. It was observed that the incidence of the disease in the various units of troops on the island bore a relation to the proximity of camps and other military installations to native villages and to the frequency of mingling of soldiers and natives at work. Our installation was situated within 50 yards of a native village, and a native house, in which lived proved carriers of filariasis, was situated within the hospital grounds. Natives going to and from the village frequently traversed the grounds. The members of the hospital unit developed an incidence of 50% in a year. Many attended the dispensary and some were regularly employed on the hospital grounds.

The men of a certain service unit were found after 12 months to be affected to the extent of 28%. This unit was located several hundred yards from native villages, but many natives were regularly employed in the work of the unit in close proximity to its own members.

In contrast with this experience, the incidence of the disease among the personnel of a group of units stationed some 5 miles from any native village was only 6% at the end of a year. The men of these units had little daytime contact with natives.

These differences in incidence are of special interest in the light of the fact that all soldiers on the island had frequent contacts after sunset with natives in the moving picture theatre, at dances, and in the villages. If the disease had been transmitted at night, one would have expected an approximately even distribution in the various military units.

Examinations of natives of the island, which are further described below, showed that many of them had typical fully developed elephantiasis. Blood smears made in a series of 100 individuals showed numerous microfilariæ in 40%. There was no discernible periodicity in this parasitemia, as microfilariæ were found at all hours of the day, as well as at night.

The commonest mosquito on the island was identified by area entomologists, from both larval and adult forms as *Aëdes scutellaris*. It was estimated that this species accounted for 95% of the large mosquito population of the island. Our experience showed that the species was clearly a day-biter. A small number of culicine mosquitoes were found which were not further identified. No example of *Culex quinquefasciatus* or *Anopheles* was discovered.

Mosquito breeding places abounded everywhere on the island, which was pockmarked with small crevices in the coral surface. Innumerable broken coconut shells helped to hold the water in these depressions. It was an impossible task to clear large areas and only very gradually were the grounds immediately about army sites cleaned up.

Diagnosis. When the patients we have described were first seen, no diagnosis could be made. As the clinical picture became clearer with the occurrence of well-marked lesions and the number of patients increased, the presence of microfilariæ in the blood of a high percentage of natives, together with a high density of a known vector, led to a tentative diagnosis of filariasis. This diagnosis was not proved, since neither microfilariæ nor adult worms were ever demonstrated in any

of our patients. We were informed that medical officers on other Pacific Islands known to be filarial had an experience similar to ours, and that, in a number of patients closely corresponding to those reported here, adult filariæ were found in sections of excised lymph nodes. We have not heard of the demonstration of microfilariæ in any Army patients of this group.

The status of skin tests, precipitin tests, and complement-fixation tests, which were not available to us, in the diagnosis of filariasis appears to be uncertain at present.

An epidemiologic basis for the diagnosis has been presented above. Close proximity over a prolonged period of time to natives carrying microfilariæ in their blood without adequate protection against the mosquito vector is to be emphasized. The relation we have described between variations in incidence and contact with natives is important.

The nature and course of the symptoms and lesions described appears to be well explained by the diagnosis of filariasis. In connection with epididymitis, the possibility of gonorrhea was studied, but the differentiation on the basis of history, lack of response to treatment, and associated funiculitis is not difficult. Funiculitis is well recognized in filariasis, but rare in other diseases. Varicoceles were found difficult to evaluate and were given no great weight. Hydroceles, which were not found among our patients, are said to be common in filariasis. The lymphangitis described above, especially in regard to its spread to instead of from, the periphery, and its persistence, is apparently highly characteristic of early filariasis. Among the troops on the island, there were many cases of streptococcal lymphangitis which was readily distinguishable by its acute severity, its centripetal spread, and its response to treatment.

A difficult diagnosis was presented by the case of a patient with pain, tenderness, and stiffness in the right lower quadrant of the abdomen. Nausea, vomiting, slight fever, and slight leukocytosis were present. Operation was performed, but the appendix was considered normal; enlarged mesenteric lymph nodes were present. It is possible that this patient had filariasis, as many other patients in the group we have described had similar symptoms and signs which, however, were less characteristic of appendicitis.

As to the course of the symptoms and lesions, the outstanding features were the persistence for a relatively long period, with marked day-to-day variations in severity, the lack of response to any form of treatment, except perhaps rest; and the frequent recurrence after an interval of freedom.

Treatment and Disposition. There is no known specific treatment for filariasis. Hence, we had to rely upon symptomatic therapy. In the acute phases, bed-rest and occasional sedatives were found to be the most effective measures. Severe pain and swelling of the spermatic cord and scrotal contents were treated to some effect by elevation and the application of an ice-cap. Acute lymphangitis was treated by elevation of the arm or leg and the application of hot, moist compresses. In most cases of lymphangitis, sulfadiazine was given without

appreciable benefit. In the intervals between acute attacks, limitation of physical exertion was both necessary and beneficial.

Reassurance of the patients, many of whom were greatly disturbed by fear of developing elephantiasis which they saw daily in natives, was found to be both important and effective. We did not encounter among our patients any severe or resistant instances of untoward mental reaction based on the involvement of the genitalia. In this connection, the soldiers were aware that natives with elephantiasis had many children.

In accordance with the policy of the Army, patients with the diagnosis of filariasis were evacuated, with no great delay and usually directly, to the United States. In some instances this was done by air, but more often by sea. Patients who had had the more severe lesions were given preference in time of evacuation over others. (Army policy further requires the restriction of individuals with the diagnosis of filariasis to duty within the limits of the United States.) It should be noted that unless these individuals develop microfilariæ in the circulating blood, they cannot be regarded as a source of infection for others.

Prognostic Indications. The prognosis of the cases we have described cannot be stated with certainty. Nevertheless, there are many indications which suggest that the likelihood of their developing severe late lesions, including elephantiasis, is small. Natives are infected repeatedly throughout their lives, beginning in young childhood. Elephantiasis, even in heavily infected populations, is rarely seen at a younger age than the twenties. Many natives, though their blood teems with microfilariæ, apparently never develop severe lesions of any sort. It is believed that the early removal of infected soldiers from endemic areas and the careful avoidance of reinfection may protect our soldiers, at least in most instances, from the late manifestations. In view of the bad psychologic effects of uncertainty and fear, it is clearly best for the individuals concerned to take as hopeful a view of the future as possible.

Suggestions for Control. On the basis of our experience, a brief discussion is given of the control of filariasis under similar circumstances. Mosquito control is the only satisfactory approach to the problem.

If adequate mosquito control is impossible and close contact with natives is inevitable, prolonged exposure in endemic areas should be avoided.

Filariasis Among Natives. A comparison of the clinical picture we have described among American soldiers with filariasis in native inhabitants of the island is of interest. The number of people on the island is unknown, since it is many years since a census was undertaken. The incidence of filariasis is also not known with accuracy. As was stated above, 40% of over 100 natives who were examined were found to have microfilariæ in their blood. We have also reported that this parasitemia was present at all hours of the day and night. Presumably the total incidence in natives is higher than is indicated by our results, since early infections are not associated with parasitemia. Moreover,

blood smears in many cases of elephantiasis among natives failed to show microfilariæ.

Some of the manifestations attributed to filariasis were seen in natives of all ages. The children of the island go naked up to the age of 8 or 10 years, so that infection must occur frequently at an early age. Microfilariæ are not found in the blood, however, before the age of 3 to 5 years. One 6 months old baby was treated surgically by us for multiple abscesses of the type described below, which is considered throughout this endemic area to be due to filariasis. Elephantiasis was seen among aged natives.

From a clinical point of view, it is remarkable that very few inhabitants of the island, even among those with elephantiasis, were incapacitated by filariasis. The large majority of natives was quite capable of regular work. As is well known, the presence of microfilariæ in the blood in itself is asymptomatic. The acute manifestations, which we have described as occurring in American soldiers, were seen in natives in only a few instances. It is possible that those who grow up on the island rapidly acquire a partial tolerance to the infection, which accounts for the absence of such manifestations.

Acute exacerbations of a type different from the picture seen in early cases, however, were frequently seen in natives. The commonly recognized picture is called filarial fever. The islanders are thoroughly familiar with these attacks, all of which they consider to be of the same nature. The symptoms closely resemble those of brief, severe influenza. The temperature sometimes rose to 103° F. Severe generalized aching, chills, and prostration were common. In 3 or 4 days the attack was over. Convalescence was notably rapid.

The peculiar abscesses which have been described as occurring in a few American soldiers, were common among natives, several hundred of them having been treated by us. In a single instance a filaria was found in an abscess. The commonest site was the internal part of the upper third of the thigh. Another favored location was under the rectus fascia in the right lower quadrant of the abdomen, where an appendiceal abscess was suspected but disproved. Unusual sites were the retroperitoneal tissue of the lumbar region and the popliteal space. This type of abscess was frequently multiple. A native who died following epileptiform seizures, was found on postmortem examination to have abscesses in the brain, under the left rectus, and in both feet.

Such abscesses developed slowly and were resorbed equally slowly. Patients became markedly prostrated and appeared "toxic." The temperature rose as high as 104° F. Pain about the abscess was severe. On examination, these abscesses were deep. For some time, they felt indurated and suggested neoplastic rather than inflammatory masses. In some cases a connection with bone was suggested at first, leading to the impression of an osteogenic sarcoma. In the course of time, abscesses were observed to soften as suppuration occurred. Because they were usually beneath deep fascial planes, they rarely pointed to the skin. In a few cases they were seen to resorb spontaneously. In general, incision and drainage were considered essential

after softening had taken place. Usually many communicating pockets were found, indicating a marked tendency to burrowing. The pus which was removed was odorless, thin, and greenish. Smears showed numerous pus cells, but bacteria were rarely present.

The principal chronic manifestations of filariasis in natives, apart from parasitemia, were lymphadenopathy and elephantiasis. The inguinal region was the most frequent site of lymphadenopathy. On physical examination, involved lymph nodes were difficult to distinguish from massive tuberculous nodes. Figure 1 shows a young adult native with severe bilateral inguinal lymphadenopathy. This case is characteristic of late involvement of filariasis.

FIG. 1.—Native with severe inguinal lymphadenopathy due to filariasis.

The pathogenesis of elephantiasis is the subject of controversy, which will not be discussed here. Allowing for the fact that early elephantiasis is often hidden by natives, a conservative estimate of the incidence is 5%. Cases were not uncommon in islanders in their twenties and thirties. As a general rule, since they have grown up with the disease, the natives can give few historical data on its development. Occasionally a story of numerous attacks of what was taken to be acute lymphangitis was obtained. One native with severe and extensive elephantiasis alleged that he had first noticed the development of the process 2 years before. More often, the first signs of the advanced lesions we saw had been observed 5 or 6 or more years earlier. Americans on the island were all impressed by the fact that

few natives were incapacitated by extensive elephantiasis. Islanders with massive enlargement of the legs frequently participated in dances.

Among the natives of both sexes, the commonest site of elephant-

FIG. 2.—Native, aged 44, with severe elephantiasis of scrotum and legs.

FIG. 3.—Native with elephantiasis of arms and scrotum and chronic inguinal lymphadenopathy.

iasis was the thigh and leg. In males, the scrotum was frequently involved, either alone or in association with the legs. Figure 2 shows a male islander of 44 years, who had the most extensive elephantiasis we saw. Lesions were alleged to have been present for only 6 years. The man was unable to walk and sat continuously in his hut, occupied in making grass mats and skirts. An operation had been attempted some 2 years before we saw the individual, but no benefit was apparent. Marked elephantiasis of the arm was rarely seen. Figure 3 shows a native with massive involvement of both arms; the scrotum and inguinal nodes are also shown to be enlarged. Elephantiasis of the breast was often seen in females, although it is rarely described. Figure 4 shows a marked case in a woman who also has elephantiasis of the right leg.

FIG. 4.—Female native with advanced elephantiasis of both breasts.

A case of some interest was that of a European trader who, after 4 years of living on islands where filariasis is endemic, developed attacks of filarial fever. These attacks recurred, according to the history, about every 3 months for over 3 years. At the end of that period, swelling of the scrotum and both legs began to appear. The febrile attacks ceased soon after elephantiasis began to develop. A futile operation had been performed on this man's scrotum before we saw him.

Summary. An account is given of the development among American soldiers on a filariasis-endemic Pacific Island of clinical signs and symptoms, which are attributed to early filariasis. Microfilariæ were

not found. The clinical picture was characterized by recurrent attacks of illness with transient lymphadenitis, lymphangitis, and swelling of the arms or thighs. Lymphangitis always spreads peripherally. There was no indication of the development of elephantiasis. Certain epidemiologic aspects of the incidence of the infection among troops are discussed. The vector is regarded as *Aëdes scutellaris*. Suggestions are given for the control of filariasis. The belief is expressed that early evacuation from the endemic region and avoidance of future exposure to further infection with the disease should minimize the danger of the development of permanent late lesions in these soldiers. Filariasis among natives of the island is briefly described. Of those examined by blood smear 40% had microfilariæ in their blood. At least 5% had elephantiasis.

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7. SUMMARY OF A 3-YEAR STUDY OF THE CLINICAL APPLICATIONS OF THE DISINFECTION OF AIR BY GLYCOL VAPORS*

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The clinical application of air disinfection by glycol vapors has been investigated for a period covering 3 winters at the Children's Seashore House in Atlantic City. A large part of this work has been reported previously in considerable detail.[1,2] These studies involved primarily the determination of the rate of incidence of respiratory infections in groups of patients whose air supply was largely disinfected, and in control groups.

This institution, a convalescent home, was selected because the prevailing conditions were peculiarly well adapted to the exhibition of the clinical effects of air disinfection. The patients were divided by age and sex into groups of 16, each of which occupied a ward. These wards were distributed on 2 floors of a building, the wards on the upper floor having the same size, position, exposure and window space, respectively, as those below them. The distribution of diagnoses did not vary markedly among the wards, so that the structure of the House provided pairs of wards, each well suited for control observations with respect to the other.

The patients were largely rheumatic or orthopedic, most of them bedfast, so that physical contact among patients was relatively small in extent. They were, however, not acutely ill, so that physical contact with nursing and attendant staff was not close. Accordingly, direct cross-infection or direct droplet hits were relatively less impor-

* These investigations were aided in part through the Commission on Air-borne Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army; Preventive Medicine Division, Office of The Surgeon-General, U. S. Army.

tant in the transmission of respiratory pathogens, and droplet nuclei and infected dust more so. Some pairs of beds were contiguous, except during a respiratory episode affecting the occupant of such a bed, and toys and books were transferred at times, although infrequently, from bed to bed.

There was no contact among patients from different wards, since each of the classes held in the schoolroom for the small number of ambulatory patients was limited to patients from a single ward.

During the warmer part of every fair day, except very cold ones, all beds were wheeled to open porches adjoining the respective wards. For the remaining part of the 24 hours the beds were in the wards, and during that part of the day a minimum of outside air was admitted to the wards, in order to conserve heat. The operation of the vaporizing units was continuous.

Methods. Propylene glycol was used as the disinfecting agent during the preliminary observations of the winter of 1941–42 and the following year. In the past winter, 1943–1944, tri-ethylene glycol was used.

The method of vaporization was the same for both agents. The glycol was kept at a constant level in an insulated beaker, which was supplied from a reservoir. In the beaker was immersed an electrical resistance coil of whatever wattage-rating and resistance were necessary to vaporize the required amount of glycol per hour, when used directly on the house line of 110 volts. A small electric fan was placed before the vaporizer in order to pull the glycol vapor stream and disperse it into the air nearby.

The degree of disinfection of air was determined by settling plate counts, the results being expressed in colonies per Petri plate. Comparisons were made in experimental and control wards, the exposure period being 30 or 60 minutes, depending on the time of day.

Determinations of the concentration of glycol vapor in air were made according to the method of Puck[3] for propylene glycol, and the method of Wise, Puck and Stral[4] for tri-ethylene glycol.

The maintenance of adequate relative humidity was not found to constitute a problem, since readings in the wards at semi-weekly intervals ranged between 30 and 40%, usually above 35%.

Plan of Experiments. In planning the experiments, the wards of the Seashore House were divided into pairs, each pair consisting of wards similarly placed on the second and third floors. Glycol was vaporized alternately, first in one ward of the pair and then in the other during successive 3-week periods, the opposite member serving as a control. Three-day intervals were allowed between periods of observations for infections in a state of incubation. All observations, therefore, involve comparisons of two similarly placed wards at the same time, the wards differing only in that one contained glycol vapor in its atmosphere. A respiratory infection was defined as a clinically recognizable episode with some objective manifestation in addition to fever. Thus a sore throat was included only if it showed an inflamed nasopharynx on examination; a "common cold," or painful ear was included only if a discharge or evidence of inflammation was present, and a cough was included only if productive.

Observations were made of the rate of incidence of respiratory infections, bacterial settling plate counts, and concentration in air of the glycol vapor.

Results. *The Incidence of Respiratory Infections.* The rate of incidence of respiratory infections was markedly lower in wards containing the glycol vapor (Table 1).

The upper respiratory infections observed included coryza, tracheobronchitis, nasopharyngitis and otitis media. In the first and third

winters, there was no marked preponderance of any of these particular diseases. During the winter of 1942–43, however, coryza accounted for a majority of all observed infections. In view of the fact that the common cold is probably caused by a filterable virus or filterable viruses, while the other diseases observed are caused by bacteria, a finer analysis of the data for that year is given in Table 2.

TABLE 1.—THE RATE OF INCIDENCE OF RESPIRATORY INFECTIONS IN EXPERIMENTAL AND CONTROL WARDS

			Respiratory infections	
Winter	Glycol used	Ward-weeks	Experimental	Control
1941–42	Propylene	8	2	16
1942–43	Propylene	54	5	100
1943–44	Tri-ethylene	19	6	16*
		81	13	132

* The actual number of 26 infections in 31 ward-weeks has been reduced in proportion to 19 weeks for comparison with the 19 ward-weeks of observations in glycol-vaporized wards.

TABLE 2.—THE DISTRIBUTION OF RESPIRATORY INFECTIONS BY DIAGNOSIS (1942–43)

	Number	
Disease	Glycol	Control
Common cold	3	79
Tracheobronchitis, Otitis media, Pharyngitis, acute	2	21

The Bacterial Population in the Air. The relative reduction in the population of viable bacteria in the air as indicated by settling plates was greater and more constant in the course of vaporization of propylene glycol than tri-ethylene under the conditions of these experiments, probably because of the narrower range between bactericidal and condensing concentrations in the case of the latter. Because of this narrow range, it was difficult to maintain a minimum concentration of tri-ethylene glycol vapor in air as much above the effective bactericidal concentration as in the case of propylene glycol with the vaporizing devices used in this study. Average values of all determinations are shown in Table 3.

TABLE 3.—THE BACTERIAL SETTLING PLATE COUNTS IN EXPERIMENTAL AND CONTROL WARDS

		Mean plate counts		
Year	Glycol	Glycol	Control	Ratio control/glycol
1942–43	Propylene*	13.4	81.3	6.05
1943–44	Tri-ethylene	18.3	75.3	4.12
	Number of counts:	114	46	
	Standard error of mean:	0.9	2.2	

* Individual counts given in original report.[3]

The Concentration of Glycol Vapor. The concentration of propylene glycol vapor in air was maintained in the neighborhood of one part in 15,000,000 (0.069 mg./liter). Concentrations at various times and in

different parts of the experimental wards ranged from 0.048 mg./liter to 0.094 mg./liter.

In the case of tri-ethylene glycol the maintenance of a satisfactory concentration presented a greater problem, because of the narrow range between bactericidal concentration and precipitating concentration mentioned above. In the absence of sensitive methods for regulating or measuring concentrations of tri-ethylene glycol vapor in air, a rate of vaporization sufficient to disinfect the air to a considerable degree was often found to produce precipitation of glycol on windows, floors and objects in the ward. The concentration of this vapor in air ranged between 0.0018 mg./liter to 0.0033 mg./liter.

The vaporization of propylene and tri-ethylene glycol in bactericidal concentrations has in these experiments been shown to cause a reduction in the total incidence of respiratory infections.

Discussion. The difficulties encountered in this study in the use of tri-ethylene glycol are due largely to the early stage of engineering development of the field and to the relatively small size of the enclosed spaces involved. In a larger volume of air, the fluctuations in glycol concentration caused by occasional opening of doors, etc., would be proportionately smaller and the concentration could be maintained in a narrower range. Because of the greater range of bactericidal concentrations of propylene glycol, it was technically the preferred glycol under the conditions of our experiments. The ultimate development of devices to regulate the rate of vaporization of tri-ethylene glycol by the concentration of the vapor present in air at the moment may obviate the difficulties we found in using this disinfectant and permit workers to take advantage of its higher disinfecting potency.

At the present writing, however, it would appear that for small spaces and in the absence of refined devices to regulate the rate of vaporization of glycol, propylene glycol is the agent of choice in small wards, offices and spaces of similar size.

In considering the application of these results to other situations, it is well to allow for the peculiarly favorable circumstances at the institution chosen for the experiments.

First, the generally inactive character of the institution and the absence of acutely ill children resulted in a considerably smaller extent of traffic into and out of the ward. Again, the patients were within the enclosed space of the ward only during the colder part of the day and at night. These factors not only reduced the total air exchange rate, but decreased the degree of fluctuations of concentration of glycol vapor in air.

The character of the patients also provided exceptionally favorable experimental conditions. Most of the children were bedfast, since the great majority were convalescing rheumatic and orthopedic patients. Of the latter, the majority were fixed in a supine position by casts, breast straps or extension weights. As a result, there was relatively much less direct contact or direct droplet hits than would be expected in a group of children, and correspondingly even a greater quantitative importance of droplet-nuclei in cross-infection. Again, in most of the

bedfast and all of the supine children, expulsion of infectious material and viable bacteria was largely in an upward direction, and the time of exposure to the glycol vapor was probably considerably longer, in general, than in other situations.

Finally, it is important that during the experimental periods in any ward, glycol vapor was present in the air supply of the subjects during all of the time spent indoors.

These favorable circumstances are, however, largely of quantitative significance. Under other conditions, a higher concentration of glycol in the air or controls on sudden shifts of masses of air into the ward or room might be necessary. The studies described here have demonstrated that the disinfection of air by glycol vapors can be successfully applied to the problem of prevention of air-borne cross-infection.

Summary. The disinfection of air by the vapor of propylene glycol and tri-ethylene glycol has been applied to the clinical problem of the transmission of air-borne cross-infection in a home for convalescent patients. A marked decrease was observed in the total rate of incidence of upper respiratory infections among those patients whose air-supply was largely disinfected by glycol vapor.

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8. EXPERIMENTAL AIR-BORNE TUBERCULOSIS*

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Air-borne Contagion of Tuberculosis in an Animal Room. If normal guinea pigs[1] are placed in individual cages in a room housing tuberculous animals, the exposed pigs acquire tuberculosis of respiratory origin as evidenced by pulmonary lesions, massive tuberculous involvement of the tracheobronchial nodes draining the pulmonary portal of entry and the absence of any disease in the mesenteric or cervical nodes draining the alimentary portal. As is well known, tuberculosis characteristically leaves the traces of its progression in the body by the involvement of the nodes draining the portal of entry.

As may be seen in Figure 1, guinea pigs situated at a considerable distance from their tuberculous room-mates acquire tuberculosis just as often as the guinea pigs placed in immediate proximity to tuberculous animals. Therefore, we may assume that the contagion is uniformly distributed in the room and, since the disease is respiratory in origin, the contagion is air-borne.

Method of Studying Air-borne Contagion of Tuberculosis in Inbred Rabbits of Varying Resistance to the Disease. A large manifold[2] is

* Aided by a grant from the Commonwealth Fund.

separated in the middle by a fine wire mesh screen (Fig. 2). On one side of the screen there is a run for artificially infected rabbits which shed tubercle bacilli in their urine. On the other side of the screen,

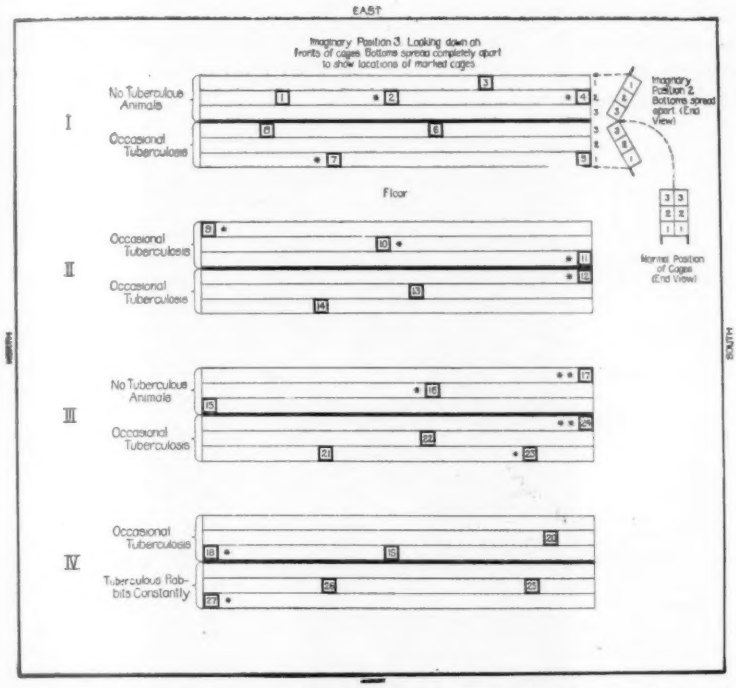

FIG. 1.—Plan of location of cages of tuberculous and non-tuberculous animals. Each asterisk indicates a guinea pig which acquired tuberculosis.

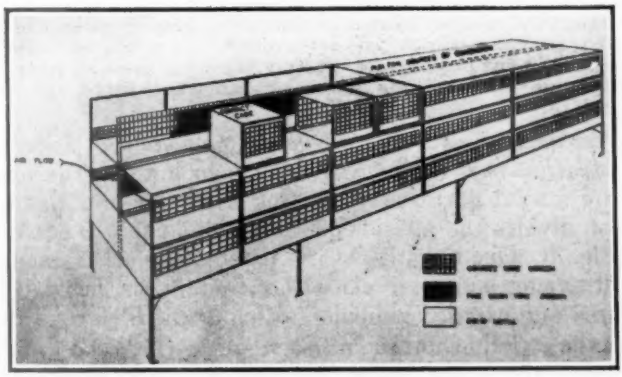

FIG. 2.—Special cages for the study of air-borne tuberculosis in rabbits.

in individual cages with open wire meshwork in back and in front, are placed members of highly inbred rabbit families. By means of tuberculin tests and Roentgen rays the onset of tuberculosis is determined. The disease thus acquired is of respiratory origin and begins as a single

primary focus in the lung, which is always associated, in animals of low genetic resistance (Fig. 3) with a massive tuberculous involvement of the draining tracheobronchial nodes and extensive hematogenous generalization. In the resistant animals (Fig. 4) the disease tends to remain localized to the portal of entry without involvement of the draining nodes and little hematogenous generalization. The disease acquired by these families closely corresponds to the different types of tuberculosis seen in man.

FIG. 3.—Organs of susceptible rabbit F4-33. Duration of disease, 3.3 months. Large, completely caseous primary focus in middle of left lung without softening. Extensive enlargement and massive caseation of homolateral draining tracheobronchial nodes. Corresponding structures on right side not involved. Large nodular caseous tubercles of hematogenous origin in both lungs. Primary, rapidly progressive, generalized tuberculosis with extensive disease in the kidneys, pleura and knee joint.

The Prevention of Natural Air-borne Contagion of Tuberculosis in Rabbits by Ultraviolet Radiation. The room housing the manifold is divided by a solid partition[3] extending from the floor to the ceiling, which also divides the interior of the manifold into 2 equal air-tight halves (Fig. 5). One room is not irradiated. The other room is irradiated. Ultraviolet lamps are placed horizontally in the space between the infected and exposed animals in each of the 3 tiers. In addition, the air of the experimental room as a whole is irradiated by ultraviolet lamps placed above and below this section of the manifold. Littermates of highly inbred families of high and low resistance are placed in corresponding positions in the contact cages of both rooms. The infected rabbits serving as sources of contagion are interchanged daily between the two rooms. Thus both the host and parasite variables are equalized.

FIG. 4.—Organs of resistant rabbit A2-6. Duration of disease, 9 months. Single, large, well-encapsulated cavity in the right lung. Draining tracheobronchial nodes normal. Tuberculosis analogous to the "reinfection type," with tubular spread to the entodermal tract, including larynx and intestines, with ulceration in the colon. Mesenteric nodes normal. Kidneys normal. Non-progressive, uniformly distributed, nodular tubercles in both lungs of hematogenous origin.

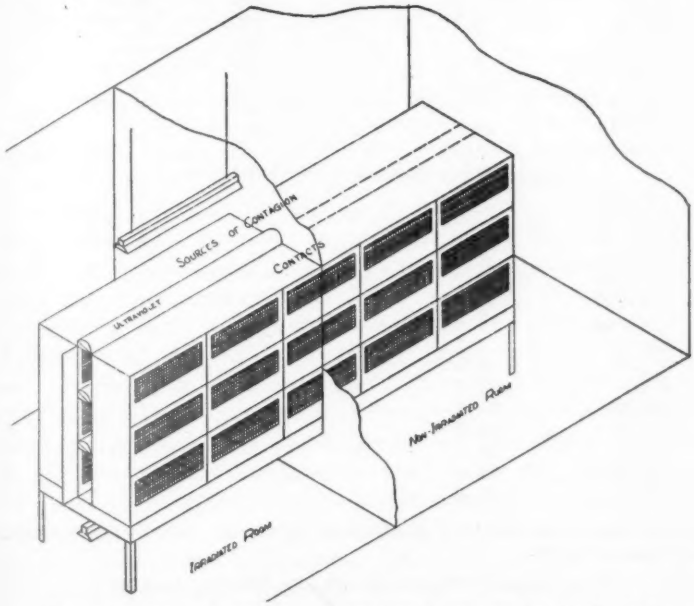

FIG. 5.—Set-up of cages of irradiated and non-irradiated animals.

At the end of a year (Table 1) 11 of the 15 contacts in the unirradiated room died of tuberculosis. These included rabbits of high and low resistance to the disease. None of the 15 litter-mates exposed to the same contagion in the irradiated room developed tuberculosis. Three additional rabbits in the control room developed tuberculin sensitivity without any tuberculous changes at autopsy. None of the protected rabbits developed tuberculin sensitivity. Only one rabbit in the irradiated room developed a regressive microscopic tubercle. Thus a 73% mortality from tuberculosis was eliminated by ultraviolet radiation. That the intensity of contagion involved in this experiment is much greater than occurs in human life can be appreciated from the fact that only 1% of human beings exposed to household contagion acquire tuberculosis in 1 year. It is probable, therefore, that ultraviolet radiation may control air-borne contagion of human tuberculosis.

TABLE 1.—THE EFFECT OF ULTRAVIOLET IRRADIATION ON NATURAL AIR-BORNE CONTAGION OF TUBERCULOSIS IN CONTACTS OF RABBIT FAMILY A, OF HIGH INHERITED NATURAL RESISTANCE, AND IN FAMILIES C AND F, OF LOW INHERITED NATURAL RESISTANCE TO THE DISEASE (EXPERIMENT OF 1942-43)

Family	Rabbit No.	Duration of exposure (mos.)	No. of times tuberculin positive	Maximum tuberculin reaction in mm.² of inflammation	Killed (K) or died (D)	Extent of tuberculosis at death
		Rabbits Exposed in Unirradiated Room				
A	A8 = 19	5.6	7	368	D	++++
	A8 = 51	6.3	7	741	D	+++
	A7 = 26	7.3	7	372	D	++++
	A8 = 43	9.7	4	475	D	0
	A7 = 31	10.8	15	1350	D	0
	A8 = 29	11.6	7	150	K	++
	A7 = 36	11.6	11	260	K	++
	A7 = 44	11.6	0	...	K	0
C	C6-9	5.2	7	1330	D	++++
	C6-32	5.7	7	432	D	++++
	C5-50	6.1	7	672	D	++++
	C6-26	9.2	2	213	D	+ =
	C6-1	11.6	3	153	K	0
F	F6-25	8.8	4	342	D	++++
	F6-14	10.4	3	141	D	++++
		Rabbits Exposed in Irradiated Room				
A	A8 = 23	6.5	0	–	D	0
	A8 = 39	8.9	0	–	D	0
	A7 = 37	11.6	0	–	K	0
	A7 = 40	11.6	0	–	K	?*
	A8 = 49	11.7	0	–	K	0
	A7 = 28	11.7	0	–	K	0
	A8 = 52	11.8	0	–	K	0
C	C6-30	5.7	0	–	D	0
	C5-44	11.6	0	–	K	0
	C6-2	11.7	0	–	K	0
	C6-13	11.7	0	–	K	0
	C6-31	11.7	0	–	K	0
F	F5-27	11.7	0	–	K	0
	F6-21	11.8	0	–	K	0
	F6-15	11.8	0	–	K	

* Guinea pig inoculation of a questionable pulmonary lesion demonstrated living, virulent tubercle bacilli.

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Resistance to Attack by Air-borne Tubercle Bacilli and Resistance to the Progress of the Ensuing Disease. One inbred family has little resistance to attack by tuberculosis[4] as indicated by the short interval between the beginning of exposure and the acquisition of a positive tuberculin reaction. Yet it succumbs to a slowly progressive, localizing disease which is of considerable duration, indicating considerable resistance to the progression of the naturally acquired disease. See Table 2.

TABLE 2.—THE RELATION BETWEEN THE RAPIDITY OF ATTACK BY NATURAL AIR-BORNE CONTAGION OF TUBERCULOSIS AND THE DURATION OF THE ACQUIRED DISEASE IN FAMILY A, OF HIGH RESISTANCE, AND FAMILIES F AND C, OF LOW RESISTANCE TO THE INFECTION

A family			F family			C family		
Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)	Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)	Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)
A8=19	0.9	4.7	F4-25	1.9	3.8	C6-9	1.3	3.9
A8=29	1.3	10.4	F4-30	2.4	3.0	C2-8	2.0	9.5
A7=31	1.8	—	F2-15	3.0	6.2	C6-32	2.1	3.6
A8=43	1.8	—	F5-2	4.6	—	C5-50	2.3	3.9
A4-4	2.0	—	F6-25	5.1	3.7	C4R-2	2.7	4.3
A8=51	2.3	4.1	F2-3	6.0	5.0	C5-30	3.0	3.3
A7=26	2.3	5.0	F5-14	6.0	—	C4S-9	3.3	tbc. + snuffles
A3=3	3.2	11.5	F4-33	6.2	3.0	C2-6	3.7	3.7
A6=21	3.3	—	F3-9	6.5	8.0	C4S-11	3.8	tbc. + snuffles
A5=3	3.3	12.9	F6-14	8.3	2.1	C4R-6	4.7	3.8
A5=4	3.3	—	F3-7	11.0	3.5	C4S-30	4.9	—
A5=21	3.3	10.7	F4-11	11.7	4.0	C2-1	5.0	3.0
A7=5	3.5	—				C6 1	5.5	—
A7=36	3.6	8.0				C2-7	7.0	5.0
A5=2	4.3	—				C6-26	8.3	tbc. + snuffles
A7=10	4.9	—				C5-14	9.0	2.6
A2=11	5.0	7.5				C2-18	11.9	—
A7=4	6.0	—						
Average:	3.1±1.3	8.3±3.1		6.1±3.0	4.2±1.7		4.7±2.8	4.2±1.8

P of pre-allergic period between A and F = 0.999.
P of duration of disease between A and F = 0.999.
P of pre-allergic period between A and C = 0.976.
P of duration of disease between A and C = 0.999.

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Another inbred family has considerable resistance against attack by natural air-borne contagion of tuberculosis as indicated by the long interval elapsing between the beginning of exposure and the onset of a positive tuberculin reaction, but the acquired disease is rapidly progressive, disseminating in type and of short duration, indicating little resistance to the progression of the naturally acquired disease. Resistance to attack by air-borne contagion of tuberculosis is therefore distinct from the resistance to the progression of the ensuing disease. "Anfälligkeit" is distinct from "Hinfälligkeit."

The Effect of Increasing Concentrations of Air-borne Tubercle Bacilli on Rabbits of High and Low Genetic Resistance to the Disease. If rabbits of high and low genetic resistance to the disease are simultaneously exposed in different experiments to increasing concentrations of air-borne tubercle bacilli,[4] the effect of this increment is different on animals of high and low resistance. The concentration of air-borne tubercle bacilli is varied by the route of infection used to inoculate the

rabbits serving as sources of contagion. Intravenous inoculation yields fewer rabbits which shed tubercle bacilli in their urine than when the rabbits are inoculated directly in the kidney. The concentration of the infectious agent can also be reduced by using peanut shells instead of peat moss as bedding for the sources of contagion. The former do not adsorb the tubercle bacilli-laden urine as well as the latter, and hence reduce the number of tubercle bacilli-laden particles thrown up in the air by the sources of contagion. The concentration of tubercle bacilli in the air can also be reduced by introducing ultraviolet lights in the room. It was found that increasing concentrations of tubercle bacilli in the environment of the rabbits of high genetic resistance to the disease increase the incidence of the infection, accelerate the rapidity of attack, and affect the essential character of the disease in proportion to the concentration of the infectious agent.

In the rabbits of low genetic resistance to the disease, up to a certain level, increasing concentrations of the infectious agent also increase the incidence of the disease and accelerate its onset. The character of the disease, however, is not affected. It remains rapidly progressive and disseminating in type. Beyond this concentration further increment of the infectious agent has no effect on the incidence of the disease, the rapidity of attack or the character of the ensuing disease.

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9. THE PRESENT STATUS OF GLYCOL VAPORS IN AIR STERILIZATION

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and

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The practical effectiveness of glycol vapors in the control of infections acquired *via* the respiratory tract depends primarily upon how large a proportion of these infections is air-borne. In man, gradually accumulating evidence indicates that air-borne transmission of such infections as measles,[31] chickenpox,[2] streptococcal infection,[1,6,7,9,18,32,33] the "common cold,"[8,12,27,30] and other infections[13,19] is sufficiently important to encourage practical attempts at air sterilization. Such control may assume the form of a direct attack upon microörganisms

in the air, of an attack upon secondary reservoirs in floor dust and bedclothing, or of a combination of these two methods. This review deals with progress which has been made in the employment of glycol vapors as an air sterilizing agent.

Laboratory Investigations With Glycol Vapors. In 1941, Robertson and his co-workers[25,26,28] announced that propylene glycol vapor was effective, in very small concentrations, against the following microorganisms, when suspended in the air: Pneumococci, streptococci, alpha and beta, staphylococci, *H. influenzæ*, *H. pertussis*, *Esch. coli*, *M. catarrhalis*, *B. subtilis*, and influenza A virus. An important advance was made when it was found that triethylene glycol acted in the same manner as propylene glycol, but in concentrations which were about one-fiftieth as great.[29] Many of these original observations have been confirmed by Henle and Zellat,[14] Henle, Sommer, and Stokes,[15] and Jennings and Bigg.[16]

Field Tests. To date, the results of three field tests are available. Harris and Stokes,[12] studying propylene glycol, and later triethylene glycol, in the ward of a children's convalescent home, encountered 100 miscellaneous respiratory infections in untreated wards, but only 5 in similar wards where propylene glycol was vaporized. Great reductions in total bacterial air counts, as measured by "settling plates," were recorded by these workers. Under the conditions of their tests, propylene glycol effected a reduction of 71%, and triethylene glycol a reduction of 97% in total air-borne bacteria. The Personnel of Navy Medical Research Unit No. 1[21] found reductions of 22 to 54% in total air-borne bacteria by propylene glycol (0.07 to 0.14 mg. per liter), but the number of tests performed was apparently very small.

In order to test the efficacy of triethylene glycol vapor upon a respiratory *pathogen* under natural conditions, the Commission on Air-borne Infections[5] conducted extensive tests upon hemolytic streptococci in army hospital wards. These investigations showed that triethylene glycol produced overall reductions of about 65% in air-borne hemolytic streptococci in scarlet fever wards and in measles wards where streptococcal cross-infections took place. However, when the vapor was employed in conjunction with oil treatment of bedclothing and floors, the reductions exceeded 90%. The combined treatment produced an atmosphere almost free of hemolytic streptococci, both during periods of ward activity and during "quiet" periods. The average concentration of triethylene glycol required to produce these results was 0.0045 mg. per liter of air.

Factors Which Influence or Augment the Efficacy of Glycol Vapors. A. Relative Humidity: Glycol action is most effective in the middle ranges of relative humidity: 35 to 50%.[22] Though some effect is produced by the vapors when relative humidity is as low as 20%, more glycol is required. At higher humidities (75% or more), the air cannot hold enough glycol to be of any value.

B. Temperature: Low temperatures enhance the action of glycol vapors; high temperatures depress their effectiveness.[22] Bactericidal action is greater below 72° F. than above this point. This temperature

effect is proof that the bactericidal action of glycols is physical rather than chemical.

C. Dust and Lint Control: As indicated above, actual field tests have shown that triethylene glycol is more effective in combination with adequate lint and dust control than when used alone.[5] This is in keeping with the observation of Robertson[24] that moist microorganisms are killed more rapidly by glycol vapor than dried organisms.

Apparatus for Dispersing Glycol Vapors. Four general types of vaporizing devices have been described:

A. Vaporization of the Liquid Glycol From a Hot Surface: This can be accomplished by any heat-producing unit, such as a radio resistor,[22] a soldering iron,[11] or an electric light bulb.[20] The vapor is then dispersed by suitably placed fans. When glycol is vaporized directly from heated surfaces, precautions should be taken to insure the temperature's remaining below the disintegration point of glycols, 260° F. Nothing is known of the toxicity of such disintegration products.

B. Passage of Air Over Revolving Evaporating Surfaces: Coey and Spiselman, of the Research Corporation,[4] have devised a vaporizer in which air is drawn past a battery of electric heaters, and then over a series of revolving evaporating disks which dip into a reservoir of liquid glycol. The glycol-laden air then escapes through a vent and is distributed by fans or through a duct system.

C. Boiling of Water-Glycol Mixtures: This method delivers both glycol vapor and water vapor into the air.[17] When heat is applied to an aqueous solution of glycol, water evaporates more rapidly than glycol, so that the glycol concentration of the solution rises. The increase in glycol concentration is associated with an elevation of the boiling point. When the temperature rises to a certain level, a thermostat opens a solenoid valve, which feeds water into the vaporizer. The water thus cools the solution to a point where the solenoid valve again closes. This instrument, described by Jennings and Bigg,[17] when set at 280° F., is calculated to deliver 0.04 lbs. glycol and 2.5 lbs. water per hr.

D. Atomization of Glycol-Water Solutions: Another glycol disperser described by Jennings, Bigg and Olson[17] utilizes, as its basic unit, a series of nozzles which spray the glycol directly into an air stream. The smaller droplets evaporate, while the larger ones are removed by a series of baffles. In practice, it is necessary to warm the air just before it passes the spray. The glycol-laden air is led into a duct system.

Maintenance of Relative Humidity. This is easily accomplished in steam-heated rooms by introducing steam directly into the room from the steam line. The hissing sound produced by the escaping steam can be eliminated by a suitable muffler. Also, the humidity can be regulated to within about 5% by inserting a solenoid valve between the steam line and the muffler, and controlling the operation of the valve by a human hair humidistat located in a convenient place in the room. Maintenance of adequate humidity in buildings where steam is not available, such as army barracks, is more difficult. So

far, no satisfactory answer to this problem has been found. Another method of raising the humidity is by boiling water-glycol solutions.[17]

Regulation of Glycol Content of Air. The ideal glycol concentration in the air is an amount just below saturation. If the level is lower than this, the bactericidal action is diminished. If it is higher, a visible fog will form. Though fogs are not harmful, they are psychologically undesirable. Puck, Wise and Robertson[23] have constructed a regulating device which automatically controls the concentration of glycol vapor in the air of a room, maintaining it just below the fog level.

Toxicity and Inflammability. Hanzlik and his co-workers have demonstrated a low degree of toxicity of oral or parenteral propylene glycol in experimental animals.[10] More important in reference to the use of glycol vapors for air sterilization has been the demonstration by Robertson and his co-workers[24] that rats and monkeys maintained for a year or more in atmospheres saturated with the vapors of propylene and triethylene glycol could thrive and bear young.

It has also been shown that no fire or explosive hazard is offered by the vapors in the concentrations required for air sterilization.[3]

Effect of Glycols on Surfaces and Fabrics. Propylene and triethylene glycol vapors are without effect upon fabrics. The vapor of propylene glycol produces tackiness on certain varnishes, but this effect has not been observed with triethylene glycol.

Conclusions. Though practical experience with the glycol vapors is extremely meagre, early reports encourage the hope that they may be of value in the control of infections acquired *via* the respiratory tract. Moreover, if the use of the vapors be combined with adequate dust control, a significant decrease in respiratory infection may result.

Practical engineering problems in the distribution of the vapor are being studied. The maintenance of an optimum glycol concentration in hospital wards has been shown to be practicable, especially when a regulating device or "glycostat" is employed. The practical use of the vapors in air-conditioning systems is under investigation but has not yet been perfected.

Though the bactericidal effect of glycol vapors is important, its virucidal action may prove to be of greater practical value. Finally, it should again be emphasized, that the final practical utility of glycol vapors, or any other control measure predicated upon the reduction of the bacterial content of the air, depends upon whether a large or a small proportion of respiratory-acquired disease is air-borne. An increasing body of evidence indicates the amount of air-borne infection is greater than was formerly believed.

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10. RECENT STUDIES ON THE CONTROL OF DUST-BORNE BACTERIA BY TREATMENT OF FLOORS AND BEDCLOTHES WITH OIL*†

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IT is now well established that individuals ill with certain infections of the respiratory tract markedly contaminate their environment with the specific etiologic agents which may survive in dust and bedclothes for long periods of time. Diphtheria bacilli,[6] staphylococci,[17] pneumo-

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† Shortly after this report was given (May 3, 1944), three papers by English investigators[1,18,37] appeared in the May 6th number of the Brit. Med. J. They contained pertinent information, relative to methods and results of controlling dust-borne infections by treatment of floors and bedclothes with oil, which has been incorporated in the present review.

cocci,[4,12] and tubercle bacilli[23] have been isolated from ward dust. The hazardous degree to which the skin, hands, wearing apparel, bedclothes and room dust can become seeded with pathogens, however, has been shown particularly in the studies of infection in wards housing patients with hemolytic streptococcal disease,[7,8,13,29,36] and from observations on the streptococcal output of healthy "carriers."[15,16]

Floor dust and bedclothes especially have been shown to harbor millions of hemolytic streptococci.[21,29] What part these "environmental reservoirs" of bacteria play in the spread of infections in barracks, wards, schools and homes, and so on, is not clearly established. The great rise in the bacterial count of the air in acute respiratory disease wards and barracks during bedmaking and floor sweeping has led an increasing number of observers to conclude that infections acquired *via* the respiratory tract from the inhalation of dust-borne bacteria[3,7,23,29] and viruses[9,19,22,32] are far more prevalent than generally recognized.

Ultraviolet light,[20] glycol vapors,[25] hypochlorous acid,[26] and so on, employed in the sterilization of air have only a limited effectiveness against dried dust-borne organisms. The development of adequate dust and lint control measures, therefore, as a means of preventing the dissemination of pathogens through the air becomes of great importance. The application of oil to floors and bedclothes for the purpose of holding dust, lint and bacteria have been found to be highly effective. Studies concerning the application and results of these methods are given in this report.

Oiling Floors. *Kind of Oil.* The specifications of the crude paraffin oil (spindle oil) used by the English investigators[28] and of the pale paraffin oil employed by the Commission on Air-Borne Infections[5,27] are essentially similar. Both meet the U. S. Government specifications,[11] which require that the flash point (open cup) shall be 300° F. or more; the viscosity at 100° F., 70 to 110 seconds; a pour point not higher than 30° F.; and a pale lemon color. The general requirements of floor oil are that it shall be clear, well refined, petroleum-oil, free from sediments and foreign material and have no objectionable odor.

Amount of Oil Required. The amounts of oil necessary to hold dust and lint depends chiefly on the kind of floor and the duration of effectiveness desired. As little as 1 gallon of oil applied per 1000 sq. ft. of wooden floor surface is sufficient to hold dust for a few days.[28] Such small amounts initially applied require oiling every 2 or 3 weeks. The duration of effectiveness of the floors to hold dust, lint and bacteria increases with each application.[28] Unfinished soft and hardwood floors can take as much as 1 gallon of oil per 150 sq. ft. The dust-holding effectiveness of such a single, large, initial application lasts for as long as 6 months, provided the floors are mopped only with warm water and not too frequently.[5] In treating smooth surfaced floors, *e. g.*, composition, linoleum, varnished and waxed, the oil should be applied in small amounts in order to avoid slipperiness and must be reapplied frequently.[5,28]

Application of Oil. Before oil is applied to floors, they should be thoroughly cleaned and dried. The manner of application depends on

how much oil is to be used. For small amounts, *e. g.*, 1 gallon per 1000 sq. ft., a cloth mop is best.[28] For larger quantities, a hair broom is most satisfactory.[5] It may also be applied as a sweeping compound mixed with sawdust.[5] Initially oiled floors, regardless of the method of application, are at first slippery and wet. A few to several hours are required for the oil to soak into the floors.

The mechanism of the dust and bacteria holding action of floor oils is a mechanical one only, and depends on the stickiness of the oiled surface.[5,28] When oiled floors are swept the dust, lint, and so on mats together in increasingly larger clumps which either roll along the floor or rise only a short distance into the air.[5,28] Floor oils have no bactericidal action. Various antiseptics and germicides have been added to floor oils without success.[33]

Control of Dust-borne Bacteria by Oiling Floors Alone. Van den Ende, Lush and Edward, 1940, were the first to call attention to the dust and bacteria holding properties of crude paraffin oil (spindle oil).[33] They carried out an experiment in which they beat blankets artificially seeded with hemolytic streptococci in two comparable rooms, one with an oiled and the other with an untreated floor. After allowing time for the bacteria to settle, blood agar plates were placed in each room and the floors were swept. The resulting collection of streptococci on the plates showed a marked reduction (89%) in the aerial contamination of the room with the oiled floor. Thomas[28] extended these observations to army canteens and hospital wards. Using the Bourdillon, Lidwell and Thomas "slit sampler" and sampling 10 cu. ft. of air he found that a single application of spindle oil (1 gallon for 1000 sq. ft.) to floors resulted in a striking and continuous reduction (80 %) for 10 days in the number of bacteria projected into the air during sweeping. Similar observations were made during dust control studies in hospital wards by the U. S. Naval Medical Research Unit No. 1.[24]

Crosbie and Wright[6] greatly reduced the air contamination with diphtheria bacilli by oiling the ward floors. Robertson and associates,[27] studying the effect of oiling floors on the bacterial content of barracks' air, observed a 70% reduction in the number of bacteria in the air in oiled floor barracks during the time the men were getting up, dressing, sweeping and making beds. Andrewes,[2] reviewing the methods of controlling the spread of infectious diseases in crowded public places, recommended strongly that wherever possible floors should be oiled to prevent dissemination of dust-borne pathogens.

Control of Dust-borne Bacteria as a Means of Preventing Respiratory Infections. Two investigations in army installations have so far been reported. Feasby and Bynoe[10] in Canada consider that adequate dust control measures such as good ventilation, sweeping the huts with oiled sweeping compounds by an orderly after the men had left the hut, were chiefly responsible for the reduction of respiratory tract infections among the men living in the dust controlled huts. Crowding was considered also to be a factor in the higher rate of their control group. Anderson, Buchanan and MacPartland[1] in England studied the control of respiratory infections by oiling floors in two army units

of approximately the same size (1300 to 1700 each) and comparable personnel, in a large training center from December, 1942, through March, 1943. Oil was applied (1 gallon per 1000 sq. ft.) to the barracks floors approximately every 4 weeks. Unit A, living in oiled floor barracks, had an average weekly respiratory infection rate of 7 per 1000 men, while in the control unit the rate was 38 per 1000 men. An outbreak of acute respiratory disease of epidemic proportions occurred in the control unit with no corresponding rise on the rate of infection in the test unit.

Oiling Bedclothes. *Application of Oil to Bedclothes.* The treatment of bedclothes with dust-laying oils for the purpose of reducing dust-borne infections in hospitals was first investigated by the English.[2,30,31,34,35] The two methods initially employed by them consisted in the impregnation of bedclothes with (1) paraffin oil dissolved in an organic solvent,[2,30,31,34] and (2) a special oil-in-water emulsion.[35] While the bedclothes treated by these two methods exhibited excellent dust and bacteria holding properties the oil preparations were, for various reasons, found to be unsatisfactory for laundering procedures. Further investigations by Harwood, Powney, and Edwards[18] of the British Laundry Research Association has resulted in the preparation of 2 oil-in-water emulsions which they found satisfactory for the oil treatment of bedclothes. They are as follows:

For Woolen Goods	Parts by vol.	*For Cotton Goods*	Parts by vol.
Technical mineral oil	20	Technical mineral oil	20
Fixanol C*	2	Teepol†	3
Water	78	Water	77

* Fixanol C emulsion is a cation-active agent of the cetyl pyridinium bromide type.

† Teepol is an anion-active agent based on the sodium salts of sulfated secondary alcohols.

The application of the oil to the bedclothes takes place as the final rinse after washing. As these emulsions are designed to cause a selective absorption of the oil by the blankets and bedclothes, the amount to be added to the laundry wheel is calculated on the percentage of oil desired in them. The quantity of oil recommended is enough to give 5% dry weight in the bedclothes. Analysis of blankets and cotton goods treated with such solutions actually were shown by analysis of the oil content to contain approximately this amount.

In field studies of the Commission on Air-Borne Infections* on the prevention of respiratory infections in army barracks by treating floors and bedclothes with oil, Robertson and associates[27] employed an oil-in-water emulsion in 1 and 2% solutions. Its formula is as follows:

	Grams
Mineral oil (Fractol A)	88.0
Oleic acid (purified)	8.9
Triethanolamine	3.9
Lecithin	0.01

* Board for the Investigation and Control of Influenza and Other Epidemic Diseases, U. S. Army.

The oil is applied to the blankets as the final rinse. When bedclothes, both woolen and cotton goods, are treated in an emulsion calculated to give approximately 5% maximum take up by dry weight of the bedclothes, from 1.5 to 4% oil is deposited in the blankets.

These two types of dilute water-in-oil emulsion formulæ described by the English workers[18] and ourselves[5] can be applied on a large scale under the direction of skilled help. Bedclothes, both woolen and cotton fabrics, containing from 1.5 to 5% oil by weight appear no different than unoiled ones, and do not constitute a fire hazard.[27]

Control of Dust-borne Bacteria by Oil Treatment of Bedclothes. Andrewes and his co-workers[2] first reported the dust-laying power of oiled bedclothes. Oiled and unoiled blanket strips were artificially infected with a coarse spray of hemolytic streptococci or staphylococci, then dried and subsequently beaten in a room, and plates exposed for 5 minutes. In the case of all-wool oiled blankets there was a 95% decrease in the number of bacteria liberated into the air. The bacterial reduction in the case of treated cotton sheets were less pronounced but significant. Van den Ende, Edward and Lush,[31] studying blankets containing from 2.3 to 6.5% oil, obtained a reduction of 90% in the amount of dust and numbers of bacteria which could be liberated from them by shaking. Oiled cotton goods (sheets) gave a 70% reduction. Further observations by Thomas and Van den Ende,[30] Van den Ende and Spooner,[34] and Van den Ende and Thomas[35] on the effect of oiled and unoiled bedclothes on the contamination of the surrounding air due to bedmaking in hospital wards, showed that oiling the bedding produced a marked reduction in the dispersion of bacteria from this source, which varied from 75 to 99% on different tests. It was found that when the bedclothes were heavily contaminated, oiling the floors had no effect on the rise in the bacterial population of the air following bedmaking.[30,34,35]

Robertson and associates[27] found that bedclothes, blankets, sheets, pillow cases, mattress covers, containing from 1.5 to 2.5% oil gave reductions in the total number of bacteria liberated during bedmaking of about 70%. They[5] also found that adequate control of dust- and lint-borne bacteria in oiling floors and bedclothes increased the effectiveness of triethylene glycol in sterilizing the ward air.

Application of Oil to Floors and Bedclothes for the Prevention of Respiratory Tract Infections. Wright, Cruickshank and Gunn[37] recently reported a 12-week study on the control of dust-borne streptococcal infections in two identical 18-bed measles wards by treating floors with spindle oil, and bedclothes with dilute oil-in-water emulsions, to give an oil content in them of approximately 5%.[18] Patients as far as practicable were admitted to test and control wards alternately. In the test ward for the first 3 weeks the effect of oiled floors alone was studied. The last 9 weeks oiled bedding, including blankets, counterpanes, sheets, pillow slips, patients' garments, towels, gowns, white coats, curtains and so on were used. In the control ward no dust control measures were employed.

As Type 6 streptococcus accounted for about 90% of the cross-infections it was used as the "indicator organisms." In the test ward

with oiled floors alone, the infection rate was 58.1%, compared with a rate of 53.3% in the control ward. The middle ear complications were the same, 18.4%, in each ward. Hemolytic streptococci, mostly Type 6, were numerous in the air during bedmaking. Thus, oiled floors alone were not sufficient to control dust-borne streptococci in measles wards.

During the last 9 weeks, when both oiled floors and oiled bedding were employed, the mean air count for hemolytic streptococci during bedmaking was reduced 97.5%. The mean hemolytic streptococcus count during sweeping was 99% less than in the control ward. The cross-infection rate was 18.6%, while in the control ward it rose to 73.3%. The middle ear complication rate due to Type 6 was 2.8%, compared to 14.3% in the control ward. In this study, the combined application of oil to floors and bedclothes appeared to control effectively dust-borne streptococcal infections in measles wards. However, the results were not entirely conclusive because (1) the contamination of the toys were not controlled, and (2) the petroleum jelly used in performing the nasal toilets of the children was contaminated with Type 6 streptococci.

The Commission on Air-Borne Infections[5] has made a study of the effect of oiling floors and bedclothes on the incidence of acute respiratory diseases in a considerable number of troops, approximately 3600 in the test and a similar number in the control barracks. The study extended over a period of 10 weeks. During this time there was an average weekly reduction of 24% in hospital admissions for respiratory diseases from the treated barracks. The reduction in hospital admissions was greatest in the test groups whose corresponding controls had a high rate of disease. Thus, where the average weekly admission rate was 30 per 1000 in the control, it was 14 per 1000 in the test groups, giving an average weekly reduction in hospital admissions of over 50%. In these groups there was also an average weekly reduction of 37% in the number of dispensary visits for respiratory infections from the test barracks.

Conclusions. 1. The application of oil to floors is a simple and economical procedure.

2. Methods for the oil-treatment of bedclothes on a large and practical scale have been reported. Much remains to be done in perfecting economical and stable oil-in-water emulsions and techniques of application which can be carried out by unskilled laundry workers.

3. There are now ample data to show that oiling floors and bedclothes are effective procedures for the control of dust, lint and dust-borne bacteria in the laboratory, hospital wards and barracks. Where bedclothes constitute the major source of aerial contamination, oiling the floors alone is not sufficient.

4. The studies reported to date on the control of respiratory infections by the use of these dust and lint control measures are favorable. Much additional data as to their advantages and limitations in relation to other preventative procedures are needed before their efficiency in controlling dust-borne infections can be accurately determined.

5. The combination of the oiled floors and bedding with air steriliza-

tion measures holds real promise for the ultimate control of air and dust-borne diseases.

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11. SAMPLING DEVICES

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The determination of the number of air-borne bacteria in a certain volume of air allows some insight into the effectiveness of factors which might control the spread of air-borne diseases. Direct proof for

the effectiveness of a control measure can be obtained only by the demonstration of a decrease in disease incidence involving long periods of study. On the other hand, information on bacterial populations subjected to certain control measures can be obtained in a relatively short time and under controlled conditions.

It is for this reason that sampling methods for the determination of the number of air-borne microörganisms have been worked out.[1–13] When by these air sampling methods a certain control measure has been found to be effective under the constant conditions of an experimental chamber in which a certain pathogen or non-pathogen has been introduced, the control measure can then be applied under field conditions and air samples again taken in order to determine whether the control measure is still effective. Epidemiologic data should, of course, be collected as a means of correlating the control measure with disease incidence.

Only under special conditions will the determination of pathogens with the help of sampling devices be possible under field conditions, because in general they represent only a small proportion of the total bacterial population. Therefore, a decrease of non-pathogens in a treated air space as compared to a control space is taken as a measure for the efficacy of the treatment.

The value of such data is determined by the validity of certain assumptions:

1. A control measure which affects most non-pathogens will also be effective on most pathogens. The factor of pathogenicity does not seem to be correlated with sensitiveness to general control measures.

2. A measure which has no effect upon non-pathogens can reasonably be assumed to be non-effective for the usual type of pathogens. When one accepts this statement, laborious and time-consuming preliminary experiments on the effect of possible control measures on pathogens can be replaced by experiments on non-pathogens following simple sampling techniques. They will enable the experimenter to decide whether a measure for controlling air-borne organisms is sufficiently promising to warrant field tests.

The determination of the number of organisms in a certain air volume is performed by samplers which follow one of two principles: impingement on solid media or atomization in liquid media.

The impinging devices which we compared are the air centrifuge, the funnel device, the slit device, the bottle device, and the sieve device. The open plate method by which organisms are collected on the media by gravity, and which we also used, can be included in this group. The atomizing methods we employed are the bead bubbler, the atomizer bubbler, and the aeroscope.

Figure 1 gives the actual number of organisms obtained with various samplers in a single experiment, and Table 1 summarizes the results of a series of similar experiments. In this table is given the number of organisms found in 10 cu. ft. of air expressed as the ratio of the number of organisms which settle in open plates exposed simultaneously for a 10-minute period.

From these and other data, it is clear that the group of atomizing devices gives bacterial counts which are 10 to 30 times higher than those of the impinging devices.

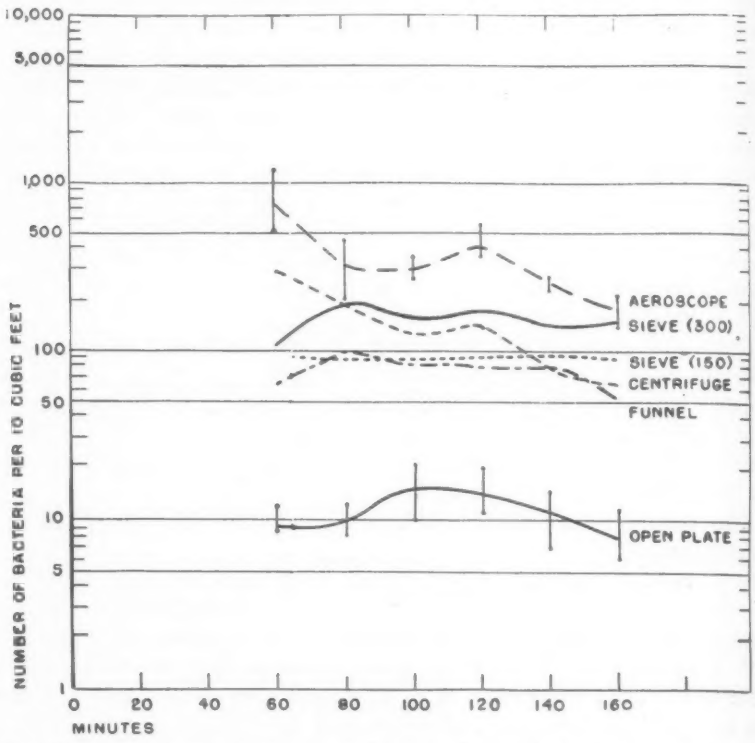

FIG. 1.—Comparison of bacterial counts of 5 sampling devices with those obtained with the open plate method (one experiment). The open plates were exposed for 10 minutes, whereas the sampling devices recorded the number of organisms in 10 cu. ft. of air. The first set of samples was taken 60 minutes after introduction of bacteria in the experimental room by means of a Graeser atomizer. The vertical lines of the aeroscope and the open plate curve indicate the numerical spread for each run. R.H. 75%, temp. 27° C. — — —, Aeroscope; ————, sieve device with 300 openings in the sieve plate; ————, sieve device with 150 openings in the sieve plate; – – – –, air centrifuge; — — — —, funnel device; ————, open plate method.

TABLE 1.—RATIO OF BACTERIAL COUNTS OBTAINED WITH VARIOUS SAMPLING DEVICES TO THE AVERAGE COUNT OF 6 TO 10 OPEN PLATES EXPOSED AT THE TIME OF SAMPLING WITH THE DEVICES

Device	No. runs	Ratio to open plate	σ of ratio	Coeff. of variability
Open plate	53	1.00		
Funnel	53	3.97	0.427	11
Bottle	15	1.88	0.296	16
Slit	21	1.94	0.701	36
Centrifuge	22	2.27	0.287	13
Atom. bubbler	18	87.07	13.160	15
Bead bubbler	34	68.23	7.470	11

E. coli sprayed in room by bubbler. R.H. 35 to 55%.

It can also be seen that among the group of impinging devices and again in the groups of atomizing devices, certain samplers give con-

sistently higher bacterial counts than others in the same group, although the differences here are much less pronounced. The differences within each group have been further studied and can be related to various differences in design, leading to a more or less complete trapping of the organisms which are carried by the air.

One cause for differences in bacterial counts of samples obtained with the impinging and the atomizing devices was eliminated in our experiments but should be considered. If micro-aërobic organisms can be expected to be present in the samples, the atomizing devices will give higher counts than the impinging devices. The micro-aërobes will be submersed in the former case, when 1 cc. of the sampling liquid is plated out per Petri dish and nutrient agar is added subsequently, whereas in the impinging devices the micro-aërobic organisms are deposited on the surface of the agar, where they may not develop. In order to determine the number of micro-aërobes present, the samples obtained with the impinging device should be taken in duplicate and half of them be covered with a second layer of agar after the sampling, thus allowing the micro-aërobes to develop.

The main cause for the differences between the impinging and the atomizing devices as groups was found to be due to the fact that the air-borne microörganisms may occur in clusters. Each cluster is counted as one colony in the impinging devices, but the clumps are more or less broken up in the atomizing devices.

Results of 4 series of experiments furnish indirect proof that the breaking up of clusters is mainly responsible for the high bacterial counts obtained with the atomizing devices:

1. When bacteria are introduced in an experimental room by an air stream which bubbles through a bacterial suspension, large clusters can be expected to occur in the air. When a Graeser atomizer is used, the large clusters will be broken up before they are introduced in the room. The bacterial counts obtained show that the ratio of atomizing devices to the open plate is higher in the first case than in the second.

2. When two sampling devices are run in series, invariably the second device will give higher counts when it is an atomizing device than when it is an impinging device. This indicates that the clusters of organisms which escape the first device are broken up in the atomizing device which is used as a second device.

3. When open plates are exposed simultaneously and for the same period, those with an agar surface invariably show significantly lower counts than those with a liquid surface, especially when this liquid is atomized after the sampling.

4. When samples of air containing a dye are taken simultaneously with an atomizing device (bead bubbler) and an impinging device (sieve device), and the color is determined photometrically, the atomizing device as shown in Table 2 is only about 2 times as efficient as the impinging device, since the dye "clusters" in the impinging device contribute as much to the final color as the broken-up dye clusters in the atomizing devices. The results obtained with the bead bubbler were not materially affected by the use of 0.3% agar in the place of water.

TABLE 2.—COMPARISON OF RECOVERY OF A SPRAYED DYE BY 4 METHODS

Device	Recovered dye in mg. per liter				
Bead bubbler with 0.3% agar	1.96	2.37	0.90	1.96	2.56
Sieve	0.77	1.02	0.42	0.95	1.33
Bead bubbler with water	2.60	2.51			
Bead bubbler with 0.3% agar	2.37	2.23			

Uranine, 20 gm. per 100 cc. meat broth, sprayed in room by Graeser atomizer and recovered by the bead bubbler and the sieve device from 6 to 10 cu. ft. of air.

From these experiments we can conclude that the difference in bacterial counts between the atomizing and the impinging devices is due mainly to the fact that bacterial clusters are broken up in the atomizing devices, giving rise to high bacterial counts, and that, on the basis of the dye experiments, these counts are only to a small degree due to a somewhat more efficient manner of air sampling by the liquid devices.

Little is known concerning the pathogenicity of air-borne microorganisms in relation to the number necessary to cause a primary infection and to the different physical forms in which they can occur, namely, in clusters or singly, in droplets or dried. These factors will certainly be different for each organism involved.

Information on the manner in which microörganisms occur in a certain air space should therefore cover the following points:

1. The total number of organisms present, whether occurring singly or in clusters. An approximation to this number is given by the atomizing devices.

2. The number of particles or droplet nuclei which contain microorganisms, either singly or in clusters, and which remain suspended in the air or are in the process of settling. This number is approximated by the impinging devices.

3. The number of particles or droplet nuclei containing microorganisms, which are heavy enough to settle through gravity. The open plate method supplies this information.

It is therefore proposed that data be obtained by methods designed to procure these three physical forms in which organisms may occur in the air. The sampling methods we believe most capable of measuring the 3 physical forms and the manner of settling of the air-borne organisms are given above, namely: (1) the open plate; (2) a representative of the atomizing methods; and (3) one of the impinging methods.

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12. MEASUREMENT OF AIR-BORNE INFECTION BY THE DISINFECTION OF AIR*

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THE papers presented at this round table indicate the dominance of air-borne infections among the communicable diseases surviving sanitary control during the last half century. Before the institution of sanitation, water- and milk-borne intestinal infections dominated our mortality from communicable disease. Only in recent years has environmental control of epidemic respiratory contagion been demonstrated.[1] Principles of sanitary control of intestinal infection may be adapted to inherent differences in the respective media and modes of spread of infection in the development of air sanitation.

Studies of air-borne infection and sanitary air control have progressed through two stages, study of the behavior of indoor air-borne parasites and the ecologic study of these parasites and their control by disinfection. The spread through the air of infection from person to persons sharing confined atmospheres and from aggregation to aggregations by persons thus exposed, distinguishes epidemics of respiratory contagion from static outbreaks of infection ingested with accidentally contaminated water, food or milk. If outside sources of contamination are not independently maintained, explosive outbreaks of intestinal infection usually cease for want of a mechanism for propagating the cases. Respiratory contagion, on the other hand, is self-propagating, waxing like fire so long as the number of susceptible persons is sufficient to maintain the case rate, and waning when this number fails, or being dramatically interrupted when changes in the conditions of spread, such as summer ventilation, dilute the atmospheric contamination per person. If summer ventilation is sufficient to cause this inter-

* Concluding discussion of round table on air-borne infection at the meeting of the American Society of Bacteriologists in New York on May 3, 1944.

† Supported by a grant from the Commonwealth Fund for study of prevention and control of air-borne infection.

ruption, it is logical to presume that equivalent ventilation, however practically obtained, would be as effective in the wintertime.

The increase in atmospheric volume per susceptible, consequent upon the opening of windows in the summertime, when air-borne infections decline, probably accounts for the longer season of epidemic spread of measles and chickenpox, found by M. W. Wells[2] in northern latitudes, where the season of closed windows is longer. A hypothesis has been advanced that the rate of elimination of indoor air-borne infection during the winter with windows closed, equivalent to that naturally provided in the summer when the windows are open, would exceed the "threshold" sanitary ventilation required to cause respiratory epidemics to wane.

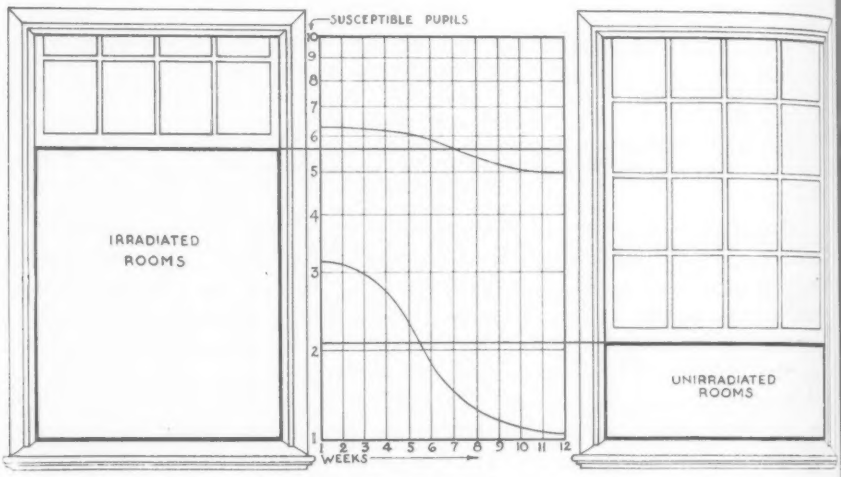

CHART 1.—Threshold sanitary ventilation.

This hypothetical relationship between sanitary ventilation and the control of spread of epidemic contagion is diagrammatically illustrated on Chart 1. The central figure shows the number of school children susceptible to measles per 300 cu. ft. of air per minute (Pennsylvania Standard for 10 pupils) in irradiated and unirradiated classrooms of the Germantown Friends School and the Swarthmore Public Schools during the 1941 epidemic. The points of inflection of the curves theoretically indicate the number of pupils provided with threshold sanitary ventilation.[3]

The difference in sanitary ventilation represented diagrammatically by the position of the window sashes is provided by radiant disinfection. Thus a wide open window would represent the ventilation required to prevent the epidemic spread of contagion. Actually the window in irradiated rooms should be shown wide open because the class cases were not contracted in the classrooms. The experimental measurement of "threshold" sanitary ventilation by radiant disinfection of air against epidemic spread of childhood contagion in schools is interpreted

by this dynamic hypothesis of air-borne infection to approximate 5 or 10 times normal winter ventilation.[3]

The hygienic interpretation of radiant disinfection into terms of equivalent ventilation requires a formulation of quantitative relationships between irradiation and disinfection. The distribution of irradiation within enclosed spaces depends upon the length of the rays, as determined by their position and direction.[4] Average intensity of irradiation (watts per sq. ft.), which corresponds to the concentration of disinfectant in chemical disinfection, may be determined by summing the products of radiation (watts) times length of rays (feet) between the source and the point at which the rays disappear from the atmosphere, divided by the volume of the enclosed space (cubic feet). This value, divided by the maximum uniform intensity obtainable from the radiation in a cubic space of the same volume, might be called the efficiency of irradiation.

Maximum disinfection of an enclosed space would be achieved if average intensity of irradiation were uniformly distributed throughout the entire space. In practice, however, it may not be feasible to expose occupants to the intensity required to disinfect. The amount of disinfection throughout the room, for a given average intensity of irradiation, is dependent upon circulation of the bacteria from the occupied to unoccupied zones.[4] The average disinfection actually achieved can be determined by bacteriologic tests, and the fraction that this represents of the maximum, which is theoretically obtainable, can be computed. This fraction might be called the efficiency of disinfection and depends *inter alia* upon the efficiency of irradiation.

The principal purpose of bacteriologic tests is to determine the average rate of removal of significant air-borne organisms from the room by sanitary ventilation. Under special circumstances, as in use of light curtains, protection may exceed the average disinfection as defined by these tests. In general, however, the concentration of light in regions away from the occupants will result in less removal of organisms en route from person to person than by average disinfection in the room. The efficiency of irradiation and disinfection described above may indicate the extent to which protection to the occupants differs from that indicated by the average disinfection determined by bacteriologic tests. It has been found in simplest cases, such as schoolrooms,[5] that with low efficiency of irradiation and disinfection, higher average disinfection would be required to accomplish approximately equal protection against classroom spread of certain childhood contagions. It was therefore proposed that the hygienic rating of disinfection be raised as the indices of irradiation and disinfection efficiencies are increased by good design.

These procedures for determining dosage apply particularly to irradiation of organisms in minute particles which drift around in the air like cigarette smoke until they are breathed into the lung, vented from the room with fresh air, or destroyed by disinfection.

The school provides a favorable opportunity for study of the tactical problem of prevention of air-borne infection within an enclosed

atmosphere. Universally spread, air-borne infections are likely to be caught early in life, and if they confer lasting immunity become contagions of childhood alone. Except for brothers and sisters attending school, the normal home tends to shelter the pre-school child from exposure until it enters the school reservoir of infection. Secondary incidence may be distinguished with a high degree of probability by the clear-cut incubation period of certain childhood contagions.

The school in a small community also favors study of the strategic problem of cutting lines of communication between aggregations. Important channels of commerce in contagion within the childhood age stratum are indicated by secondary infection uncomplicated by multiple infections in the various atmospheres to which adults are exposed.

Experiments have within the epidemiologic limitations of school studies, evaluated some of the important foci of spread of air-borne contagions of childhood. A mumps epidemic at Swarthmore showed the possibility, under special circumstances, of a community epidemic among school children in spite of winter protection of the primary school. Epidemiologic analysis of secondary incidence disclosed the need, in such special cases, of extending coverage of school children beyond the school.

Germantown Friends School studies had already indicated the futility of trying to stop colds among school children by irradiating only their classrooms. These universal infections involve multiple infection in every type of aggregation, and their control requires broader coverage than does childhood contagion. The community control of upper respiratory infection, to which all ages because of temporary immunity are susceptible, will require blockade of the important channels of commerce in air-borne infection by covering the dominant foci. The public health strategy of reducing respiratory disease therefore seeks the atmospheres within which multiple infections occur and attempts to cover a major fraction of those atmospheres.

The problem may be approached experimentally by selection of large regimented groups in which exposure to unprotected atmospheres is limited. Men in military units are more exposed to each other within limited atmospheres than to men in other units, and similar opportunities may exist in civil life. It may come about, however, that the rapid growth of applied air disinfection will not wait for such studies, but will proceed to cover normal communities until the extent and importance of air-borne infection will be manifested, just as the importance of intestinal infection conveyed by water and milk was demonstrated by widespread use of water purification and milk pasteurization.

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THE INCIDENCE OF SICKLEMIA AND SICKLE CELL ANEMIA IN 3000 CANAL ZONE EXAMINATIONS UPON NATIVES OF CENTRAL AMERICA*

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The incidence of sicklemia and sickle cell anemia has been determined by many investigators for most regions of the United States. Lewis,[7] summarizing many of these reports, reaches an over-all incidence of 7.48% sicklemia and finds that of the people showing sicklemia 2.5% will show sickle cell anemia. Archibald,[2] Russell and Taylor,[11] and Smith[12,13] have reported cases of sickle cell anemia from the Sudan (1 case—Arab), Gold Coast (1 case), and Nigeria (4 cases) diagnosed on the classic histologic picture of the spleens from autopsies. They give no studies of the incidence of sicklemia in their reports. Pons and Oms[10] found 5.29% to be present in Puerto Rico. Ortiz[8] reported on 7 people of one family in Puerto Rico, 3 having sickle cell anemia, and the other 4 having sicklemia. Zerbino *et al.*[16] reported a typical case of sickle cell anemia occurring in a 2½ year old mulatto female in Argentina; they gave no studies on the incidence of sicklemia. Weiss *et al.*[15] reported 2 cases of sickle cell anemia from Peru; they gave no studies on the incidence of sicklemia. In Cuba, Cabrera Calderin *et al.*,[3] Chediak *et al.*,[4] and Alonso-Patino *et al.*[1] have reported cases of sickle cell anemia with no studies of sicklemia. A Cuban boy with obvious negroid features, who was living in the United States, was reported by Stewart[14] as having sickle cell anemia. Herrick's[6] original classic description of sickle cell anemia was on a young negro male, studying in Chicago, who was born in the British West Indies. Pawan[9] reported a case of sickle cell anemia from Trinidad, B.W.I., in a male mulatto, and remarks that although no studies of the incidence of sicklemia were made, "in the course of routine blood examinations for malarial parasites and the Widal test, sickle cells have been seen, which is not surprising in a population with a high percentage of negro blood."

There have been no reports of sickle cell anemia or sicklemia from the Canal Zone or the Republic of Panama, and it is the purpose of this paper to report the incidence of sicklemia and sickle cell anemia in this region, based upon autopsy, hospital and native village studies.

Material. The material for this study was obtained from three sources. Since 1935 in the Board of Health Laboratory a routine procedure at the autopsy of all mestizo, brown and black people has been the preparation of petrolatum-sealed wet blood films. These films are kept at room temperature and examined for "sickling" by either the intern or resident on the Pathology Service after 24 and 48 hours. All preparations that are questionable or positive for sickled erythrocytes are examined by the pathologist for the final decision. It is therefore possible that in a few cases sickled cells may have

* Read in part at the 442nd meeting of the Medical Association of the Isthmian Canal Zone, Sept. 21, 1943.

been overlooked, but we can be sure that all cases designated as showing "sickle cells" are reliable. In all, 1595 consecutive autopsy specimens of blood were examined in which the data and the conditions necessary for this study were suitable.

The second source of material was made possible through the kindness of Dr. H. C. Clark* and his associates in allowing and assisting me in the collection of 628 sealed wet blood films from the villages used in his malaria control program. These specimens were examined by me after 24 and 48 hours. The third source of material is from the examination of 777 mestizo, brown and black admissions to the wards of Gorgas Hospital. The collection of this material has extended over a period of 6 months, with the sealed wet blood films also being examined by me after 24 and 48 hours.†

It has been impossible in the hospital and native population groups to determine with any degree of accuracy the racial grouping. However, in the autopsy cases the race could be determined accurately from the information upon the death certificate. In none of the autopsy cases was an attempt made to determine the race by color, facial appearance, name and so on. The information taken from the death certificate is filled out from official Canal Zone records in the majority of instances and by Panamanian officials in the other instances. The classification as to race in the autopsy series was achieved in the following manner: A person born of parents born in the British West Indies is considered a British West Indian, whether born in the Republic of Panama or in the British West Indies; this same procedure is true in all of the racial tabulations in Tables 1, 2 and 3. In the mixtures, the parents were born in the respective countries listed, irrespective of where the child was born. Thus, for example, a child born in the Republic of Panama of a father who was born in the Republic of Panama and a mother who was born in the British West Indies is regarded as a mixture of the British West Indian and Panamanian races.

In Table 1 is given the racial distributions of 1595 autopsy cases examined for the presence of sickled erythrocytes. Of the 1595 examinations, 154 (9.6%) showed sickled cells in proportions ranging from 5 to 100% of the preparation. The total numbers examined in all but the first two groups, namely, the British West Indians and the Panamanians, are too few for use in drawing conclusions. However, it is of interest to note the presence of sicklemia in Colombians, in British West Indian-Panamanian mixtures, in Colombian-Panamanian mixtures and in British Hondurians. The very finding of 2 United States negroes showing sickled cells in a total of 4 examined is ample warning against drawing any further conclusions from these smaller groups.

In Table 2 the 998 British West Indians and the 372 Panamanians examined are broken down into race-sex-age and sickled-nonsickled groups. It is apparent that there are no great differences between the British West Indians and the Panamanians. The over-all incidence of sicklemia (10%) in the combined group is comparable with the higher figures of the many studies reported from the United States ranging as they do from 4.3 to 15%.[7] In this study we find a consistently higher percentage incidence in females as compared to

* A complete description of the villages is given in one of the papers dealing with malaria control methods.[6]

† The autopsy series of blood examinations reported here was stopped when the examination of patients' blood in this hospital was started, although we still prepare routine sealed wet blood films at autopsy for examination.

males and this is borne out in the study of the native population. Likewise Pons and Oms[10] in their studies in Puerto Rico found a much higher incidence in females.

TABLE 1.—RACIAL DISTRIBUTION AND INCIDENCE OF SICKLED ERYTHROCYTES IN 1595 AUTOPSIES

Race	Total number examined	Number showing sickled cells	Percentage where significant
British West Indian (B.W.I.)	998	96	9.6
Panamanian (Pan.)	372	42	11.2
Colombian	66	6	9.1
B.W.I. and Pan.	55	3	
Colombian and Pan.	24	1	
Salvadorian	16	0	
British Hondurian	11	4	
Costa Rican	8	0	
Ecuadorian	6	0	
Peruvian	6	0	
United States negro	4	2	
Costa Rican and Pan.	4	0	
Mexican and Pan.	4	0	
Cuban	3	0	
Nicaraguan	2	0	
Ecuadorian and Pan.	2	0	
Venezuelan	2	0	
Chinese and Pan.	2	0	
Indian	2	0	
African	2	0	
Cuban and B.W.I.	1	0	
Nicaraguan and B.W.I.	1	0	
Venezuelan and Pan.	1	0	
Costa Rican and B.W.I.	1	0	
Colombian and Cuban	1	0	
Puerto Rican	1	0	
Totals	1595	154	9.6

It is of interest to consider the positive cases found and the percentage of sickling according to age groups in the combined race-sex columns (see the last two columns in Table 2). It is seen that more cases of sicklemia occur in the autopsy age groups of 40 and below, although the majority of the 1370 cases are found in the age groups beyond 40 years. No appreciable differences in the causes of death could be determined between those patients showing no sicklemia and sicklemia at autopsy, except, of course, where sickle cell anemia was the cause of death. Thus, for example, the incidence of tuberculosis was no higher in the sicklemia group than in the non-sicklemia group when compared by ages.

In the 154 cases of sicklemia, 14 cases of sickle cell anemia diagnosed by the clinical history, laboratory studies, and autopsy findings were found. Thus, the incidence of sickle cell anemia in 1595 autopsies was 0.9%, and the incidence of sickle cell anemia in the sicklemia autopsies was 9%. The usual statement[1] is that 2.5% of all people having sicklemia will show sickle cell anemia. In Table 3 is given the race-sex-age distribution of these cases. Eight of the cases occurred in British West Indians, 6 in Panamanians; 5 were males, 9 females. The youngest case was 1 month; the oldest was 49 years.

TABLE 2.—INCIDENCE OF SICKLED ERYTHROCYTES AT AUTOPSY IN BRITISH WEST INDIANS AND PANAMANIANS (1370 CASES)

Age groups	British West Indians (998)									Panamanians (372)									Total both groups (1370)								
	Male sickling			Female sickling			Male and female sickling			Male sickling			Female sickling			Male and female sickling			Male sickling			Female sickling			Male and female sickling		
	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%	Neg.	Pos.	%
1– 6 mos.	3	2	..	6	..	..	9	2	..	19	4	..	25	1	..	44	5	..	22	6	..	31	1	..	53	7	11.6
7–12 mos.	2	1	..	1	..	..	3	1	..	13	1	..	7	2	..	20	3	..	15	2	..	8	2	..	23	4	14.8
1– 5 yrs.	6	..	..	7	..	..	13	..	..	35	4	..	27	8	..	62	12	..	41	4	..	34	8	..	75	12	13.8
6–10 yrs.	1	..	..	2	2	..	3	2	..	9	1	..	4	..	..	13	1	..	10	1	..	6	2	..	16	3	15.7
11–20 yrs.	16	1	..	14	5	..	30	6	..	13	3	..	7	4	..	20	7	..	29	4	..	21	9	..	50	13	20.6
21–30 yrs.	29	2	..	18	7	..	47	9	..	52	2	..	18	2	..	70	4	..	81	4	..	36	9	..	117	13	10.0
31–40 yrs.	34	4	..	16	5	..	50	9	..	28	2	..	8	3	..	36	35	..	62	6	..	24	8	..	86	14	14.0
41–50 yrs.	144	14	..	54	5	..	198	19	..	25	3	..	10	1	..	35	4	..	169	17	..	64	6	..	233	23	8.9
51–60 yrs.	256	20	..	59	8	..	315	28	..	14	..	..	3	..	..	17	..	..	270	20	..	62	8	..	332	28	7.7
61–70 yrs.	111	15	..	35	1	..	146	16	..	6	..	..	2	..	..	8	..	..	117	15	..	37	1	..	154	16	9.4
71–80 yrs.	51	2	..	17	..	..	68	2	..	2	1	..	1	..	..	3	1	..	53	3	..	18	..	..	71	3	4.0
81+	10	1	..	10	1	..	20	2	..	1	..	..	1	..	..	2	..	..	11	1	..	11	1	..	22	2	8.3
Totals	663	62	8.5	239	34	12.4	902	96	9.6	217	21	8.8	113	21	15.6	330	42	11.2	880	83	8.6	352	55	13.5	1232	138	10.0

TABLE 3.—SICKLE CELL ANEMIA IN 1595 AUTOPSIES

Age groups	British West Indians		Panamanians	
	Male	Female	Male	Female
1– 6 mos.	1	..	1	
7–12 mos.	..	..	..	1
1– 5 yrs.	..	..	2	1
6–10 yrs.	..	1		
11–20 yrs.	..	1	..	1
21–30 yrs.	..	3		
31–40 yrs.	..	1		
41–50 yrs.	1			
Totals	2	6	3	3
	8		6	

In the native villages of the Republic of Panama (Table 4) a total of 628 sealed blood preparations satisfactory for examination were obtained. In this group were 293 males and 335 females. A total of 41 preparations showed sickled forms; 12 males and 29 females. As the total number of males and females examined are approximately even, the marked preponderance of sicklemia in females found in the autopsy group is borne out in the native population and is of significance. The incidence of sicklemia in the entire group was 6.5%. In the males it was 4.1%, and in the females, 8.6%, or double that of the males. It was impossible to obtain reliable information from any source regarding their racial origins; they are known to be intermarried in variable degrees, to British West Indians used during the construction of the Canal and others coming in before that time.

TABLE 4.—INCIDENCE OF SICKLEMIA IN NATIVE VILLAGES, REPUBLIC OF PANAMA

Name of village	Number examined	Males	Females	Showing sicklemia		
				Number	Males	Females
New San Juan	154	61	93	8	2	6
Gatuncillo	38	18	20	2	0	2
Los Guacos	9	4	5	0	0	0
Agua Clara	34	20	14	2	1	1
Santa Rosa	39	21	18	8	2	6
Guayabalito	48	26	22	5	3	2
La Laguna	86	39	47	0	0	0
Mendoza	146	79	67	4	1	3
Camaron	74	25	49	12	3	9
Totals	628	293	335	41	12	29

Percentage sicklemia . . . . males 4.1
Percentage sicklemia . . . . females 8.6
Percentage sicklemia, males and females 6.5

From the routine admissions of mestizo, brown and black patients to the wards of Gorgas Hospital 777 sealed wet blood films were studied. Of these, 56 (7.2%) showed sickled erythrocytes. In these 56 patients a diagnosis of sickle cell anemia was made in 2 males and 1 female, an incidence of 5.6%. In this study 700 males revealed sicklemia in 47 instances (6.7%) and 77 females in 9 instances (11%).

By combining the autopsy, native village and hospital figures, a

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total of 3000 examinations (male and female) were made with 246 instances of sickled erythrocytes (8.2%) in this large series.

Tabulating according to sex, from Tables 2 and 4 and the hospital examinations, we have a total of 1956 males showing sickled cells in 142 instances (7.2%). Likewise, for females we have 819 examinations showing sickled forms in 93 instances (11.35%).

Conclusions. 1. The examination of 1595 sealed wet blood films obtained at autopsies on mestizo, brown and black people dying in the Canal Zone and the Republic of Panama revealed 154 instances of sickled erythrocytes (9.6%).

2. In the 154 instances of autopsy sickled cells, there were 14 cases of sickle cell anemia (9%). Sickle cell anemia was present in 5 of 83 males and 9 of 55 females showing sickled cells. The incidence of sickle cell anemia in the 1595 autopsies is 0.9%.

3. The racial distribution of the cases examined is almost entirely from Central and South America and represents the first reported study of the incidence of sicklemia and sickle cell anemia from this area.

4. In the autopsies, 96 (9.6%) of 998 British West Indians showed sickled cells. British West Indian males showed sickled cells in 8.5%; females, 12.4%.

5. In the autopsies, 42 (11.2%) of 372 Panamanians showed sickled cells. Panamanian males showed sickled cells in 8.8%; females, 15.6%.

6. In 628 preparations obtained in native villages in the Republic of Panama, 41 (6.5%) showed sickled cells. Males showed 4.1%; females, 8.6%.

7. In 777 routine admissions to Gorgas Hospital of mestizo, brown and black patients, 56 (7.2%) showed sickled erythrocytes. A diagnosis of sickle cell anemia was made in 3 instances (5.6%) of those showing sickled forms. Males showed sickled forms in 6.7%; females, 11%.

8. Combining the autopsy, native village and hospital figures, 3000 examinations were made with 246 instances of sickled cells (8.2%).

9. Tabulation according to sex reveals sickled cells in 7.2% of males and 11.35% of females.

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STUDIES OF PLASMA VOLUME IN THE HUMAN BEING

COMPARATIVE RESULTS OF REDUCTION OF PLASMA VOLUME, INTRAMUSCULAR PRESSURE AND VENOUS PRESSURE IN SURGICAL SHOCK

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SINCE the report of the Special Investigation Committee[23] on Surgical Shock and Allied Conditions, during World War I, studies on plasma volume changes in human beings suffering from the effects of shock have been meagre. Our present concept of the reduced plasma volume in shock dates back to the report of the above committee. The well controlled animal experiments of Blalock and others,[1] showed that a reduction in plasma volume accompanies secondary shock.* The severity of the symptoms of peripheral circulatory failure in man is considered to be proportional to the reduction of plasma volume.[7] However, a number of other investigators have demonstrated that the shock state is not necessarily or quantitatively related to changes in plasma volume.[3,5,6,20,22]

Based on the spectacular effectiveness of plasma and serum in the treatment of shock in man, is the generally accepted assumption that such treatment, and the clinical improvement that follows the use of plasma, is due to a restoration of the reduced circulating blood volume. However, actual blood volume studies and data on human beings after the administration of plasma are meagre. The paucity of such studies on plasma volume of human beings made before operation prior to the inception of postoperative depression and at the appearance of surgical shock, hence warrants the reporting of data on such studies.

Methods. Plasma volume determinations were made on 7 persons. These were among the group of 97 patients in whom the dynamics of the venopressor mechanism was also being studied. The sequences in the failure of the venopressor mechanism associated with the appearance of peripheral circulatory failure have been reported elsewhere.[13]

The plasma volume was determined by the blue dye (T-1824) method of Gregerson and Gibson.[8] The dye was allowed a minimum of 30 minutes for mixing and distribution after injection, and the curve of the dye disappearance was always determined. The recheck determinations were made with a fresh injection of the dye.

The concentration of the dye in the serum was determined with a Lumetron photoelectric colorimeter. This instrument which employs 2 photoelectric cells is capable of a high degree of accuracy. In our determinations, 4 to 5 cc. of plasma were used for each determination in a cell of 1 cm. thickness. The error in plasma volume determinations was 1% (25 cc. in 2500 cc. of plasma volume). The hematocrit was determined in Wintrobe tubes.[25] Arterial pres-

* Surgical, hemorrhagic (oligemic, or hematogenic) shock and the delayed effects of trauma[2] are all grouped as secondary shock. [It should be noted, however, that "secondary shock" is often used in a more restricted sense.—ED.]

sure was obtained with a mercury manometer. Venous and intramuscular pressure measurements were made by the gravity flow method in recumbency, previously described in an earlier article.[9] The error of the method has been discussed.[10]

TABLE 1.—POSTOPERATIVE CONVALESCENCE. APPENDECTOMY
(Comparative Blood Volume and Venopressor Mechanism studies to Determine the Effect of Paredrine, 20 Mg. Subcutaneously)

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
8:35	..	2727	5097	46.5				
9:05	..	2727	5125	46.8				
9:16	..	..	..	..	112	14.4	118/90	86
9:32*	0	..	..	..	112	12.8	120/80	80
9:35	..	..	..	..	118	12.5	128/76	80
9:40	..	..	..	..	112	12.7	150/80	70
9:45	..	..	..	..	115	13.3	160/88	68
9:50	18	2727	5004	45.5	..	13.8	164/88	68
9:55	23	..	..	..	..	14.1	190/100	66
10:14	42	2727	4958	45.0				
11:00	88	2798	5041	44.5	118	12.8	108/68	95

C. B. Control No. 1. Group 1. There was no significant change in either the blood volume or in the venopressor mechanism.

* Paredrine 20 mg. (H) subcutaneous.

TABLE 2.—COMPARATIVE BLOOD VOLUME AND VENOPRESSOR MECHANISM STUDIES TO DETERMINE THE EFFECT OF PAREDRINE 40 MG. SUBCUTANEOUSLY

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
9:09	..	3030	5855	48.5				
9:47	..	3030	5827	48.0				
9:55	..	..	..	..	72	7.5	120/70	84
10:01*	0							
10:16	15	3030	..	..	64	8.6	160/82	70
10:25	24	..	..	..	63	9.4	180/110	68
10:31	30	3030	5827	48.0	61	9.6	194/112	68
10:45	44	..	..	..	66	9.0	190/112	68
11:00	59	..	..	..	60	6.0	170/105	70
11:25	84	3030	5855	48.5	56	5.8	130/72	78

J. M. Control No. 2. Group 1. There was no significant change in the blood volume. Paredrine in suitable dosage increases venous pressure but does not affect intramuscular pressure.[15]

* Paredrine 40 mg. (H) subcutaneous.

Results. Four of the 7 persons studied were normal individuals on whom the plasma volume was determined incidental to studies on the influence of other drugs[15] (Tables 1 to 4). These patients, who served as controls, showed no alterations in the plasma volume, in the venous pressure, or in the intramuscular pressure during the experiment.

Three patients were studied after major surgical procedures with and without attendant loss of blood during the operation (Tables 5, 6, 7). The plasma volume figures of these 3 patients were of interest because they showed: in the 1st patient (Table 5), the features of rapidly developing surgical shock; in the 2nd (Table 6), the effect of hemorrhage and rapidly developing peripheral circulatory failure; and in the 3rd (Table 7), the effect of surgical operation without undue loss of blood and with a minimal of postoperative depression.

TABLE 3.—COMPARATIVE BLOOD VOLUME AND VENOPRESSOR MECHANISM STUDIES TO DETERMINE THE EFFECT OF PAREDRINE 30 MG. SUBCUTANEOUSLY

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
8:06	..	2655	5206	49.0				
8:36	..	2655	5009	47.0				
8:56	..	2655	5310	50.0				
9:15	..	..	..	..	89	9.8	120/70	80
9:20*	0							
9:25	5	..	..	..	88	9.9	200/110	50
9:30	10	2655	5474	51.5	94	15.1	210/110	50
9:40	15	..	..	..	88	14.1	220/112	68
9:45	20	2655	5533	52.0	81	13.6	200/96	76
10:06	41	..	..	..	82	11.8	185/104	72
10:45	80	..	..	..	82	10.2	150/90	76
10:55	90	2655	5310	50.0	83	10.2	156/90	72

M. Control No. 3. Group 1. There was no change in blood volume. Paredrine increases venous pressure but does not affect intramuscular pressure.[15]

* Paredrine 30 mg. (H) subcutaneous.

TABLE 4.—POSTOPERATIVE CONVALESCENCE. BRODIE'S ABSCESS
(Comparative Blood Volume and Venopressor Mechanism Studies to Determine the Effect of Nikethamide 10 Cc. Intravenously)

Time	Elapsed time after Nikethamide	Plasma vol. (cc.)	Total blood vol. (cc.)	Intramuscular pressure in mm. water	Venous pressure in cm. water
A.M.					
8:12	..	2440	4207	96	11.4
9:42*	0				
9:52	10	..	..	113	19.0
10:09	17	2440	4207	97	13.7

N. M. Control No. 4. Group 1. The blood volume remained unchanged. The venopressor mechanism was heightened, intramuscular and venous pressure both increased, after nikethamide.

* 10 cc. Nikethamide intravenously.

The patient in Table 5 showed all the clinical features of surgical shock immediately following a cholecystectomy. A small quantity of blood was lost during the operation. There was *no change in the plasma volume when clinical shock was evident.* The intramuscular pressure, however, showed a marked decrease. Any considerable reduction in the plasma volume did not occur until late in the course of events, 10 hours 3 minutes after the operation. Peripheral circulatory failure

TABLE 5.—CHOLECYSTECTOMY. STORMY POSTOPERATIVE COURSE WITH EARLY APPEARANCE OF SURGICAL SHOCK
(Comparative Blood Volume and Venopressor Mechanism Studies. Demonstrating the Failure of the Venopressor Mechanism in Surgical Shock, and Its Treatment With Nikethamide)

Time	Elapsed time in min. from beginning of operation	Elapsed time postoperative	Plasma vol. (cc.)	Decrease in plasma vol. (cc.)	Total blood vol. (cc.)	Decrease in total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Change in intramuscular pressure in mm. water	Venous pressure in cm. water	Change in venous pressure in cm. water	Arterial pressure in mm. mercury	Remarks
A.M.													
7:15	..	...	..	..	..	..	..	..	..	..	..	..	First dye injected
7:46	..	...	2480	..	4350	..	43.0						
8:55	..	...	..	..	..	..	..	..	..	..	..	..	Anesthesia
9:03	0	...	..	..	..	..	..	77	..	14.4			
11:15	132	...	..	..	..	..	..	25	(−)52	7.5	(−)6.9	..	5% glucose I.V. 10:30 A.M.
11:37	144	0	2460	(−)20	4300	(−)50	..	..	..	..	..	75/50	Operation finished; patient in shock
P.M.													
12:00	..	...	..	..	..	..	42.8	..	..	6.9	(−)7.5		
12:42	..	...	..	..	..	..	43.0	33	..	7.7			
12:46	..	1 hr. 9 min.	..	..	..	..	..	..	..	..	..	..	Nikethamide, 10 cc. I.V.
12:50	..	...	..	..	..	..	..	95	(+)70	13.9	(+)7.0		
1:00	..	1 hr. 33 min.	2392	(−)88	4200	(−)150	43.0	92	..	9.0	..	..	Clin. impr. evident
2:30	..	...	..	..	..	..	..	56	..	..	..	85/54	700 cc. glucose between 1 and 2:30 P.M.
8:23	..	8 hrs. 46 min.	2239	(−)241	4070	(−)280	45.0	55	(−)40	4.4	(−)9.5	98/60	Pulse 132; signs of shock
8:35	..	...	..	..	..	..	..	55	..	4.7			
8:55	..	...	..	..	..	..	..	41	(−)54	4.3	(−)9.6		
9:20	..	...	..	..	..	..	..	..	..	..	..	..	Nikethamide, 5 cc. I.V.
9:24	..	...	..	..	..	..	..	75	(+)34	10.1	(+)5.8	100/68	
9:29	..	...	..	..	..	..	..	75	..	7.6	..	96/60	
9:40	..	10 hrs. 3 min.	2064	(−)416	3621	(−)729	42.8	80	..	6.0	..	94/64	Clinically improved; symptoms of P.O. depression with adequate peripheral circulation
A.M.													
9:10*	..	...	..	..	..	..	..	51	..	5.4	..	..	Condition satisfactory

Surgical shock was clinically evident with no change in plasma volume. Intramuscular pressure, however, showed a marked drop early in the course of events. The maximum decrease in intramuscular pressure coincided each time with the appearance of peripheral circulatory failure. Clinical improvement coincided with the heightening of the venopressor mechanism after the use of Nikethamide. Clinical improvement was obtained after Nikethamide despite the loss of at least 416 cc. of plasma volume. The clinical course coincided with the direction of the changes in intramuscular pressure, rather than with the alterations in plasma volume.

* 1st P.O. day.

TABLE 6.—HYSTERECTOMY. LARGE LOSS OF TOTAL BLOOD VOLUME FROM HEMORRHAGE DURING THE OPERATIVE PROCEDURE. RAPIDLY APPEARING SHOCK

the loss of at least 416 cc. of plasma volume. The clinical course coincided with the direction of the changes in intramuscular pressure, rather than with the alterations in plasma volume.

* 1st P.O. day.

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TABLE 6.—HYSTERECTOMY. LARGE LOSS OF TOTAL BLOOD VOLUME FROM HEMORRHAGE DURING THE OPERATIVE PROCEDURE. RAPIDLY APPEARING SHOCK

(Comparative Blood Volume and Venopressor Mechanism Studies. Demonstrating the Failure of the Venopressor Mechanism After Surgical Operation With Hemorrhage, and the Treatment of Shock With Nikethamide and With Blood Transfusion)

Time	Elapsed time in min. from beginning of operation	Elapsed time post-operative	Plasma vol. (cc.)	Change in plasma vol. (cc.)	Total blood vol. (cc.)	Change in total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Change in intramuscular pressure in mm. water	Venous pressure in cm. water	Change in venous pressure in cm. water	Arterial pressure in mm. water	Remarks
A.M.													
8:45	..	..	2940	..	5250	..	44.0						
9:30	0	..	..	..	..	..	..	96	..	6.6	..	175/94	Anesthesia, ethylene-ether
9:43	13	..	..	..	..	..	..	96	..	11.3	(+)4.7		
10:14	44	..	..	..	..	..	..	82	(−)14	27.1	(+)20.5	155/105	Trendelenburg position
10:17	47	..	2350	(−)590	4122	(−)1128	43.0	..	..	..	..	158/105	
10:30	60	..	..	..	..	..	..	57	(−)39	15.9	(−)11.2	158/105	
10:33	63	..	2345	..	4114	..	43.0	60					
11:30	120	0	..	(−)323	..	(−)738	..	..	..	..	..	..	Transfusion of 500 cc. whole blood completed
11:37	..	..	2617	(+)272	4512	(+)398	42.0	40	(−)56	3.6	(−)23.5	125/70	Peripheral circulatory failure evident
P.M.													
12:45	..	..	..	..	..	..	..	..	..	..	..	..	1000 cc. 5% glucose administered
2:00	..	..	..	..	..	..	..	..	..	..	..	..	400 cc. whole blood transfusion completed
4:00	..	4 hrs. 23 min.	3090	(+)745	5660	(+)1546	45.4	..	..	..	..	..	Clinical condition good
12:15*	..	..	2740	(−)200	4567	(−)683	39.5	47	..	6.5	..	138/92	Clinical condition good

Intramuscular pressure showed a significant decline early in the course of events, and preceded the appearance of peripheral circulatory failure. A loss of 590 cc. of plasma volume, and 1128 cc. of total blood volume was not accompanied by clinical signs of shock. Although intramuscular pressure was beginning to drop, the venopressor mechanism had not failed. The maximum decline in intramuscular pressure, and failure of the venopressor mechanism coincided with clinical evidences of peripheral circulatory failure. This, despite a restoration of 272 cc. of plasma volume by the use of a 500 cc. whole blood transfusion. The restoration of 745 cc. plasma volume from the use of 900 cc. whole blood transfusion, however, coincided with clinical improvement. A decrease of 200 cc. plasma volume on the 1st postoperative day was present with an adequate peripheral circulation. The venopressor mechanism was also compensated. The clinical picture of peripheral circulatory failure coincided with the failure of the venopressor mechanism rather than with the loss of plasma volume of 590 cc. A restoration of 745 cc. of plasma volume through the use of 900 cc. whole blood transfusion, coincided with improvement in the clinical picture.

* 1st P.O. day.

was evident when the patient was examined 144 minutes after the beginning of the operation. The plasma volume figures were 2480 and 2460 cc., respectively. At 132 minutes, intramuscular pressure was measured and found to have dropped 52 mm. to a low level of 25 mm. water. Venous pressure had dropped 6.9 cm. from the compensated high level attained during the operation.

TABLE 7.—RETROPERITONEAL SURGICAL PROCEDURE. RIGHT NEPHROPEXY
(Comparative Blood Volume and Venopressor Mechanism Studies)

Time	Plasma vol. (cc.)	Decrease in plasma (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury
A.M.							
7:30*	3000	..	5357	44.0	67	5.8	
10:50†	..	..	..	..	60	5.8	110/80
11:34‡	2795	(−) 205	5480	49.0§	60	5.8	

Retroperitoneal operations show a minimal of postoperative depression.[14] Despite a loss of 205 cc. of plasma volume, the clinical condition of the patient was good and there was no evidence of peripheral circulatory failure. Intramuscular pressure remained unchanged before, during and after the operation. The venopressor mechanism did not fail.

* Preoperative.
† At end of operation.
‡ 44 minutes after operation. Clinical condition good. No evidence of inadequacy of the peripheral circulation.
§ Possible error in hematocrit?

Uncompensated peripheral circulatory failure was still evident 69 minutes after operation when Nikethamide* (10 cc.) was given intravenously. Clinical improvement followed, and was accompanied by an increase in intramuscular pressure to 95 mm., and of venous pressure to 13.9 mm. water. The peripheral circulation was still compensated at 93 minutes (postoperative) when the plasma volume was found to be 2392 cc., 88 cc. less than the preoperative level. Intramuscular pressure was now 92 mm., and venous pressure 9 cm. water. The patient's condition was satisfactory.

The clinical condition of the patient gradually deteriorated, and 8 hours and 46 minutes after the operation he again showed the signs of peripheral circulatory failure. The plasma volume had now dropped 241 cc. below the preoperative level. Intramuscular pressure had fallen 40 mm., to 55 mm. water, and venous pressure 9.5 cm. from the heightened level attained after the administration of 10 cc. of Nikethamide 8 hours earlier, to the absolute value of 4.4 cm. water. At this point, Nikethamide (5 cc. intravenously) was again given to be followed by clinical improvement for a second time. The intramuscular pressure increased to 75 mm. and venous pressure to 10.1 cm. water, a rise of 34 mm. and 5.8 cm., respectively, from the low levels of the last previous observation. Twenty minutes later the plasma volume was 2064 cc., a decrease of 416 cc. since the operative pro-

* Coramine-Ciba (brand of Nikethamide) was used throughout our studies.

cedure; intramuscular pressure was 80 mm. and venous pressure 6 cm. water. The clinical condition of the patient was good despite the reduction of 416 cc. in plasma volume.

The maximum reduction in plasma volume occurred 10 hours and 3 minutes after surgical shock was first manifested. The plasma loss was 416 cc., yet the clinical condition of the patient was that of the usual postoperative depression with a compensated peripheral circulation. His condition was considered satisfactory. Clinically, the situation was now no different from that commonly seen in other patients after operation who demonstrated only the usual loss of vitality and weakness without failure of the peripheral circulation.[14]

The patient in Table 6 showed an early decline in the plasma volume. In 47 minutes from the beginning of the operation the total volume had declined from 5250 to 4122 cc., and the plasma volume from 2940 to 2350 cc., a decrease, respectively, of 1128 and 590 cc. Despite this loss of blood, the condition of the patient was still good. The intramuscular pressure was 82 mm. water, still within the normal range, but had decreased significantly from the preoperative level. An increase in venous pressure to 11.3 cm. water was found 13 minutes after anesthesia. In the Trendelenburg (head down position) at 47 minutes, venous pressure was recorded at 27.1 cm. water. Following a transfusion of whole blood, the plasma volume increased 272 cc. At 127 minutes after operation, failure of the peripheral circulation was unmistakable despite this increase of plasma volume. The patient was in shock. Arterial pressure had dropped 50 mm. mercury, intramuscular pressure 56 mm. water, and venous pressure 23.5 cm., from the heightened level previously attained in the head down position. The increase in plasma volume did not prevent the appearance of circulatory failure, which in turn coincided with the lowest points reached by intramuscular and venous pressure. It is significant that *intramuscular pressure declined 16 minutes before the venous pressure.*

Following a second transfusion of whole blood, the total and plasma volumes were increased to preoperative levels at 4½ hours after the operation, and the clinical condition of the patient was satisfactory.

The next day, a fresh injection of the dye showed the plasma volume to be 200 cc. less than the preoperative value. Intramuscular and venous pressures had increased above the lowest points of the previous day, and were within a physiologic range. The patient showed the usual 1st day postoperative depression of vitality. Paradoxically, although the plasma volume was reduced, the clinical condition was good and there was no evidence of peripheral circulatory failure. The patient proceeded to make an uneventful recovery without further treatment for shock.

The patient shown in Table 7 underwent a right nephropexy operation. Forty-four minutes after the operation he showed a loss of plasma volume of 205 cc. Despite the reduction in plasma volume, his clinical condition was excellent and he showed no signs of peripheral circulatory failure, and little of the loss of vitality seen in the postoperative state.

*The intramuscular and venous pressures did not change from the preoperative level.**

Discussion. These findings on plasma volume came as a complete surprise to us. Our concept of the relation of the loss of plasma volume to the clinical manifestations of peripheral circulatory failure in man is based largely on studies carried over to human beings from animal experiments, chiefly in the dog. It can be safely said that a reduction in the circulating volume of plasma in both the dog and in the human being is one of the significant and constant features to be found *late* in the course of progressively developing shock.

Much confusion has been engendered as to the cause of the conditions found in the course of well developed shock in the human being, through the failure to study these on man himself. Wiggers[24] has repeatedly emphasized the hazards of transferring the results of animal experiments to man. There can be little doubt that the earliest phenomenon in traumatic shock in dogs is a reduction in blood volume. But this need not be so in human beings.

It appears from our study that a reduction in plasma volume need not be an early change, or an initiating factor in surgical shock or in shock following hemorrhage and surgical operation in the human being; that peripheral circulatory failure can be evident without any reduction in plasma volume; and that a certain degree of decrease in plasma volume can exist without producing circulatory failure. It is also evident that a reduction in plasma volume will be found late in surgical shock.

We are in a sad state of ignorance as to the factors which lead to the inception and production of peripheral circulatory failure in man. Part of this may be due to the failure to study adequately the dynamic factors of the peripheral circulation in the human being. All attention until recently has been focused on the reduced plasma volume and on treatment aimed at the restoration of blood volume. It is even questionable whether the well deserved popularity of human plasma in the treatment of shock is effected through a restoration of lost blood volume beyond that which the volume of plasma given adds to the circulation. Human plasma however, has a marked pressor effect on intramuscular pressure.[10] It seems proper to review at this point some of the known facts of the dynamics of the peripheral circulation as related to changes in intramuscular pressure in man.

A marked drop in intramuscular pressure, which reached its maximum within the 6th to 12th postoperative hour, was consistently found after surgical procedures.[11] Uninterrupted serial readings of intramuscular and venous pressure made during and after operation and to the development of surgical shock have been reported.[12,14] The earliest and first phenomenon noted either during operation or preceding the onset of surgical shock was *a decline in the level of intramuscular pressure.* This occurred from 20 to 60 minutes, usually at 45 minutes, after the operation was begun. The decline in venous

* During our investigations, retroperitoneal operations showed the least postoperative depression or alterations in intramuscular pressure.[14]

pressure always *followed* that of the intramuscular pressure by from 16 to 50 minutes. The former time was noted in rapidly developing shock which happened on the operation table. The fall in venous pressure was noted 32 minutes before the signs of peripheral circulatory failure appeared. During the usual operative procedure, the initial decline of venous pressure followed that of intramuscular pressure within an interval of 50 minutes. The lowest points attained by intramuscular and venous pressure occurred after the initial decrease, and coincided with the appearance of peripheral circulatory failure. This was true whether or not the pressures dropped rapidly or were delayed, and the symptoms and signs of shock appeared early or late. Those patients who showed only a severe depression after operation, subtlely developed peripheral circulatory failure between the 6th and 12th postoperative hour, when it was noted that intramuscular and venous pressures had coincidentally attained their maximum point of decline. The peripheral circulation immediately after operation appeared adequate, but subsequently the clinical picture became indistinguishable from that seen in those who developed shock rapidly. In both instances venous pressure as low as 1 cm. water and intramuscular pressure down to 18 mm. water have been recorded.

The lowest level to which intramuscular pressure falls in shock and before death is 18 mm. water.[13]* The resistance of the muscle mass to the injection of saline does not decrease below this pressure immediately after cessation of the heart beat and of the circulation in clinical death in the human being and in the frog (*Rana pipiens*). *An intramuscular pressure of 20 mm. water in the resting muscle represents a complete absence of muscle tonus.*†

The alterations in intramuscular and venous pressure noted above in the review of the dynamics of the venopressor mechanism during and after operation, showed a constant coinicidence between: (1) the loss of muscle tonus, (2) then of venous pressure, and (3) the appearance of peripheral circulatory failure.

These phenomena were also seen in both patients in Tables 5 and 6. In the one, intramuscular pressure was found to have fallen to a low level 132 minutes from the beginning of the operation, when shock

* The range of variation was 18 to 24 mm. water (actually 18 to 24 mm. normal saline). Because of the possible variant in the method of measurement of intramuscular pressure, we regard 20 mm. water as the level of intramuscular pressure during life which represents a complete absence of the property of living muscle called tonus.[13]

† This is the level of intramuscular pressure found in death[13] when muscle tonus has disappeared.[16] During life, the isometric contractions of discrete muscle bundles, in the muscle at rest, serves as a microscopic pump to propel venous blood to the heart. The tonic activity of the great mass of skeletal muscle of the body thus constitutes a venous pump, just as important to the circulation as is the heart itself.[18] The loss of muscle tonus spells failure of the peripheral circulation just as surely as does left ventricular failure for the arterial circulation, and for the circulation at large. When the measurement of intramuscular pressure (which is a measurement of muscle tonus during life) indicates a level wherein tonic activity is practically non-existent, the forces which constitute the venous pump are no longer active. The peripheral circulation must decompensate when intramuscular pressure fails and the venopressor mechanism becomes inefficient.

The vascularity (the number of open capillaries and venules) in a muscle is related to the number of discrete muscle bundles in contraction at any given moment.[21] In

was first evident. An intramuscular pressure of 25 mm. water, showing practically a complete absence of muscle tonus, was found at this time. There was no change in the plasma volume even though peripheral circulatory failure was obvious.

During the 10-hour period that plasma volume progressively declined, the peripheral circulation twice showed clinical signs of failure, and was twice restored and compensated after the administration of Nikethamide. The changing condition of the patient corresponded to the direction of the changes in intramuscular pressure, and not to those in the plasma volume.

In the second patient (Table 6), sufficient interval observations were obtained to show the decrease in intramuscular pressure, preceding that of the venous pressure. In both patients, the maximum decline in intramuscular and venous pressure for each episode coincided with the onset of peripheral circulatory failure and not with the moment of the maximum decrease in the plasma volume. Compensation of the peripheral circulation which occurred twice after the use of Nikethamide in patients (Table 5) and for each spontaneously on the first postoperative morning, coincided with an increase in intramuscular pressure from a low level to above 40 mm. water. Clinical improvement was evident despite lowered values for plasma volume.

Other studies[10] have shown that plasma has a most remarkable pressor action on intramuscular pressure. Just as decreasing increments of intramuscular pressure preceded a loss of venous pressure and of the appearance of peripheral circulatory failure, studies on the effect of human plasma showed that increasing increments of intramuscular pressure preceded a rise in venous pressure. Rising increments of intramuscular pressure precedes a restoration of a failed circulation. Intramuscular pressure values below 40 mm. water, when increased above this value, were found to be followed by clinical improvement and a heightening of the venous pressure to within the normal. These phenomena were also noted in this study.

The absolute increments of intramuscular pressure are not diagnostic or prognostic in the shock syndrome, except when intramuscular pres-

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tetanic contraction, the muscle is gorged with blood. During rest, there are always a number of discrete muscle bundles in isometric contraction, open capillaries and venules, and a flow of blood. *When tonic activity has ceased, there should be no blood flowing through the muscle.* Evidence for this is furnished by observations at the autopsy table and on shock that occurred during a surgical operation (L. G.). In death from shock due to explosive missiles, the biceps and abdominal muscles were bloodless and so dry that they literally crackled when cut. In surgical shock during an abdominal operation, the cut surfaces of the abdominal rectus muscle did not ooze blood as ordinarily occurred in patients in good condition under anesthesia.

In death from traumatic shock, the muscles possessed no tonus and were bloodless. Similarly, when intramuscular pressure during life had fallen during surgical shock to the level that likewise indicated an absence of muscle tonus, blood no longer flowed from the cut muscle. On the other hand, after a restoration of muscle tonus in surgical shock, empty veins became full and venous pressure rose, indicating a reëstablishment of peripheral blood flow. In the muscle in death, and in the living muscle during shock, an important force that contributed to the mechanism of the venous pump, *muscle tonus*, was no longer present. The failure of the venopressor mechanism and cessation of the peripheral circulation occurred together.

sure has not changed from the normal preoperative level. We have never seen the clinical picture of shock in patients whose intramuscular pressure remained at the preoperative value, nor have we ever observed patients with peripheral circulatory failure on whom measurements of intramuscular pressure did not show either a decline from a previously recorded figure or an absolutely low level. It is the relative loss of the pressure of the muscles from a high to a lower level that appears to be an important factor in the loss of venous pressure and the appearance of the peripheral circulatory failure that follows. Likewise it is the relative fall in venous pressure from a high to a lower level that precedes the appearance of circulatory failure. This fits in with the findings of Holt,[19] who showed that venoconstriction may maintain peripheral venous pressure as measured in the antecubital vein in the face of a marked fall in venous pressure in the auricle. Any observed fall in venous pressure at the periphery, as from a compensated high level to a lower one *must* reflect a considerable decrease in central or auricular pressure and of venous flow. Henderson[17] also stressed the significance of a relative drop in venous pressure in the head-down position as an indication of a failing venous return. In this position, the blood returning from the tissues is, so to speak, poured into the great veins near the heart (the preventricular reservoir of von Recklinghausen). A falling venous pressure in this position indicates a lessened flow of blood to the preventricular reservoir. The rapid decline in venous pressure from a compensated high level during operation was seen in both patients in Tables 5 and 6 preceding the onset of peripheral circulatory failure. In one it occurred while the patient was still in the head-down position.

Intramuscular pressure values within the normal range are always associated with venous pressures within the normal range. We have never witnessed a marked drop in venous pressure with a normal or a high intramuscular pressure, nor have we observed a low venous pressure without a low intramuscular pressure.

Henderson[17] stoutly championed the idea that venous flow cannot be maintained and blood returned to the heart without a secondary or booster pump within the venous side of the circulation. The action of the diaphragm and the abdominal muscles, and the negative intrapleural pressure have long been recognized as factors that maintain and assist in the flow of blood to the auricle. These, plus the energy of intramuscular pressure, are the forces that constitute the venous pump. Of these, intramuscular pressure, or the intrinsic pressure and tonic activity within the muscles, is the factor of fundamental importance. It is the efficiency of the venous pump, *i. e.*, the presence or absence of muscle tonus that determines whether or not the peripheral circulation will come to a standstill, rather than changes in circulating volume. This, he has pointed out, is the mode of death in shock.

Our studies indicate that: (1) Within certain limits, a considerable reduction of circulating blood volume is compatible with an efficient venous circulation, providing that intramuscular pressure, one of the forces important in the dynamics of the peripheral circulation, is held

at an adequate level. (2) A physiologically effective venopressor mechanism coincided with an adequate peripheral circulation; one that has failed, with the appearance of surgical shock. (3) A normal peripheral circulation coincided with a normal and unchanged level of intramuscular pressure, even in the presence of a reduced plasma volume. (4) Human plasma has a decided pressor action on intramuscular pressure. (5) Nikethamide also has a marked pressor action on intramuscular pressure. The pressor action of plasma is slow, requiring 70 to 100 minutes, and the administration of 750 cc. before its pharmacologic action becomes manifest. The effect of Nikethamide, on the other hand, is very rapid. It likewise heightens the venopressor mechanism, but within 5 to 10 minutes after its administration in doses of 5 to 10 cc. intravenously, as contrasted to the 70 to 100 minutes required for plasma. (6) The presence or absence of the dynamic factors of the venous circulation (first, the relative levels of intramuscular pressure, and later that of venous pressure) corresponded more closely to the appearance or regression of peripheral circulatory failure than did changes in the plasma volume of less than 590 cc. (approximately 2 units of plasma).

The chief lesson to be derived from our studies is that greater emphasis must be placed on investigations of the dynamics of the peripheral circulation rather than upon the volume of blood that is available for the circulation, and this must be done at the bedside.

Summary and Conclusions. 1. Peripheral circulatory failure in surgical shock may be evident with a normal and unchanged plasma volume.

2. A decrease in plasma volume up to 590 cc. is not necessarily followed by peripheral circulatory failure.

3. Change in the clinical condition of the patient, for the worse or for the better, and the presence or absence of peripheral circulatory failure, coincide more closely with decline of, or the heightening of, intramuscular pressure, than with changes in the plasma volume.

4. Peripheral circulatory failure may be manifest with a normal or with a decreased plasma volume, but not with an unchanged intramuscular pressure, which remains in the normal range. The circulatory failure is always associated with a lowered level of intramuscular pressure.

5. An inadequate peripheral circulation, despite a plasma volume decrease of at least 416 cc., can be compensated and returned to adequacy with the restoration of a low intramuscular pressure to a higher level by the use of Nikethamide.

6. Changing increments of intramuscular pressure are an important factor in the dynamics of the peripheral circulation.

7. The kinetics of the peripheral circulation as related to intramuscular pressure (the venopressor mechanism) and other forces that may constitute the venous pump in man, are worthy of greater attention in investigations of the problem of shock; these studies must be made on the human being, preferably, rather than on other animals.

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ABERRANT ATRIO-VENTRICULAR CONDUCTION IN A CASE SHOWING A SHORT P-R INTERVAL AND AN ABNORMAL BUT NOT PROLONGED QRS COMPLEX*

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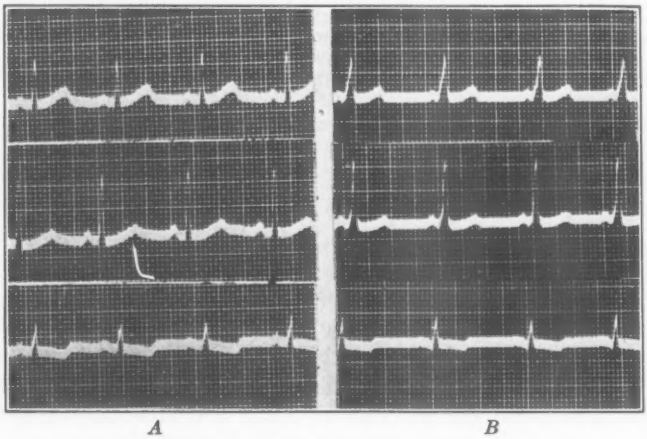
The recent cardiologic literature displays considerable interest in the subject of the Wolff-Parkinson-White syndrome. This is largely due to the physiologic considerations involved. Of the various contributions to the subject 2 are outstanding: (1) Butterworth and Poindexter—on the experimental production of the syndrome of apparent bundle branch block with short P–R interval,[1] and (2) Wood, Wolfert and Geckeler[7]—who furnished histologic proof of the existence of accessory conduction connections between the auricles and the ventricles of a patient with this type of electrocardiographic abnor-

* Read at the May meeting of the New York Heart Association.

mality.[1] The original hypothesis to explain the mechanism of this syndrome as advanced by Holzman and Scherf[4] and Wolferth and Wood[3] is as follows: some hearts possess, in addition to the normal conduction system, an aberrant pathway connecting one of the auricles with one of the ventricles; through this aberrant pathway early stimulation of one of the ventricles is achieved; the spread of excitation to the other ventricle is the cause of the prolonged QRS complex.

In a recent paper, Fox, Travell and Molofsky[2] presented a case of Wolff-Parkinson-White syndrome in which the abnormally wide QRS complex could be *further* widened by the administration to the patient of drugs with cholinergic properties, and *narrowed* considerably by the use of atropine sulfate. It was thus shown that the QRS complex in this syndrome is not necessarily a stable structure, and that its duration could be influenced by providing more "vagus substance" or by inhibiting the functional activity of this substance.

A further step in the study of this syndrome was afforded by a case recently observed at the Hospital for Joint Diseases.



A *B*

FIG. 1.—*A*, The only normal tracing obtained in the course of observation. The QRS duration is about 0.04 sec. The tracing is apparently the result of quinidine. *B*, The abnormal tracing. Note that the duration of the QRS complex is about 0.08 sec.

Case Report. A 52 year old painter was admitted with the chief complaint of pain in the left hip region. He also had occasional mild discomfort in the precordium, not accentuated by effort. A diagnosis of monostotic Paget's disease of the left ilium was made. An ECG taken on admission revealed a short P–R interval and a QRS complex of about 0.08 sec. (Fig. 1*B*). It was thought at the moment that the tracing represented a nodal rhythm. Another glance at the ECG however, revealed the presence of a slur on the upstroke of R_1 and R_2. It then occurred to us that the ECG may possibly represent a *modified* Wolff-Parkinson-White syndrome.

The patient was followed for a period of 1 year. About 75 tracings were secured and all of them, with the exception of those which were the result of special studies, presented the same structural characteristics: a short P-R interval and an abnormal QRS complex of normal duration.

Special investigations were instituted in accord with the methods previously

employed.[2,3] The drugs used in an attempt to influence the electrocardiographic pattern were as follows: quinidine sulfate, digitalis, prostigmine methylsulfate and atropine sulfate.

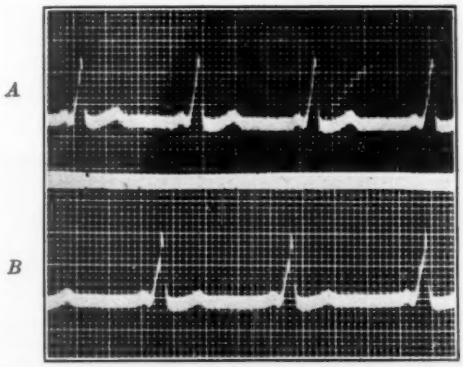


FIG. 2.—The effect of digitalis on the duration of the QRS complex. *A*, Lead I of a tracing secured immediately before the administration of Digitalin-Nativelle. *B*, Lead I of a tracing obtained 6 hours after oral administration of 1.2 mg. of Digitalin-Nativelle. Note a definite widening of the QRS complex.

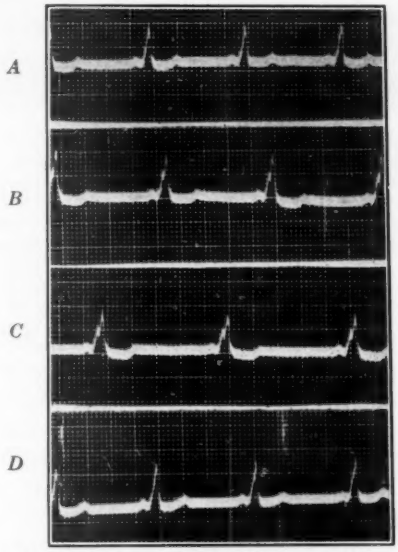


FIG. 3.—The effect of digitalis and prostigmine on the duration of the QRS complex. *A*, Lead I of a tracing obtained after 7 cat units of digitalis leaf were given over a period of 3 days. *B*, Lead I of a tracing obtained 3 days later in the course of which 8 additional cat units of digitalis leaf were given. Note definite widening of the QRS complex. *C*, Lead I of a tracing secured 20 minutes after intramuscular administration of 2 cc. of a 1:2000 solution of prostigmine methylsulfate. The drug was given immediately after tracing *B* was obtained. Note width (and form) of the QRS complex. *D*, Lead I of a tracing taken 21 days later. Note that duration of the QRS complex is that of the predominant type. Shortening of the QRS complex is apparently due to the elimination of digitalis.

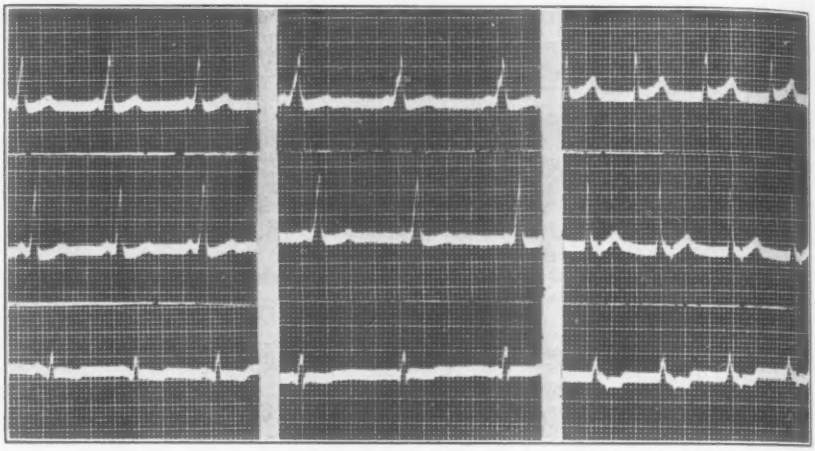
Quinidine in various doses was administered orally on 4 occasions. On 1 occasion 10 gr. of the drug was given at 7 A.M. and a similar dose at 10 A.M.

At 11 A.M. a normal sinal tracing was obtained (Fig. 1*A*). This was the only normal ECG obtained in the course of observation.

Digitalis was administered 6 times. The result was *conspicuous* widening of the QRS complex (Fig. 2*B* and 3*B*).

Prostigmine was given intramuscularly on 3 occasions. The result was a widening of the QRS complex (Fig. 3*C* and 4*B*).

Atropine was administered intravenously once, shortly after the administration of prostigmine. The result was a nodal rhythm(?) (Fig. 4*C*).



A *B* *C*

FIG. 4.—The effect of prostigmine and atropine on the form of the QRS complex. *A*, Control tracing obtained immediately before the administration of prostigmine. *B*, Tracing obtained 20 minutes after the intramuscular administration of 2 cc. of prostigmine methylsulfate, 1:2000 solution. *C*, Tracing secured immediately after the intravenous administration of atropine sulfate, $\frac{1}{75}$ gr. The drug was given immediately after tracing *B* was developed. Note change in rhythm. The QRS complexes are of the supraventricular type and resemble the normal sinal picture in Figure 1*A*.

Comment. The effect of cholinergic drugs (including digitalis), atropine sulfate and quinidine sulfate on the syndrome of short P–R interval and prolonged QRS complex was discussed in detail in 2 previous papers.[2,3] The purpose of this report is to show that prolongation of the QRS complex is not an essential criterion of the Wolff-Parkinson-White syndrome. The classical picture of the syndrome was reproduced in our case by making more "vagus substance" (acetylcholine) available. In other words, the difference between the case presented here and the classical picture of the Wolff-Parkinson-White syndrome is quantitive rather than fundamental in nature. The duration of the QRS complex is apparently, as stated elsewhere,[2,3] an expression of the degree of A–V node depression, caused by available "vagus substance."

The ECG pattern in our case could be looked upon as the resultant of the sinal impulse traveling down to the ventricles through 2 pathways simultaneously: the normal A–V conduction system, and an aberrant atrio-ventricular conduction mechanism. Depression of the A–V node by cholinergic drugs causes the sinal impulse to travel through the aberrant pathway exclusively; earlier arrival of the stimu-

lus to one of the ventricles registers a short P–R interval, but the asynchronous excitation of the two ventricles produces a prolongation of the QRS complex in the ECG. Quinidine, on the other hand, has a greater affinity for the aberrant conduction tissue, depressing it and thus causing the impulse to travel through the A–V node exclusively, describing in the ECG a normal sinal pattern.

The prerequisite for the Wolff-Parkinson-White syndrome is the presence in the human heart of a congenital anomaly, an aberrant atrio-ventricular pathway. This may be the reason why the majority of the cases reported are in the younger age group. Our patient never had an ECG tracing done prior to his admission to the hospital. But even the assumption that his ECG was previously normal does not exclude the possibility of a dormant aberrant pathway. It is conceivable that a circulatory difficulty of the A–V node due to coronary sclerosis may sufficiently depress its functional activity to permit the aberrant mechanism to take over some of the conduction function.

The explanation of the *nodal rhythm* (?) in Figure 4*C* is not simple. "If the auriculo-ventricular node is partially released from the influence of the vagus nerve, while the sinus node is still relatively under the control of this nerve, a nodal rhythm may appear spontaneously." This is the explanation given by Wilson in his paper on "The Production of Atrio-ventricular Rhythm in Man After the Administration of Atropine."[5] Another possible explanation in this case is as follows: Atropine relieves the A–V node from the influence of the vagus nerve. Conduction through the A–V node is accelerated so much as not to register a P–R segment. The P wave following the QRS complex is an expression of retrograde conduction through the aberrant A–V pathway.

Summary and Conclusion. A case is presented with a short P–R interval and an abnormal but *not prolonged* QRS complex. Prolongation of the QRS complex was achieved through the influence of cholinergic drugs. In this manner the syndrome of short P–R interval and prolonged QRS complex was reproduced. It would therefore appear that the width of the QRS complex in this syndrome is merely an expression of the quantity of "vagus substance" available, and that the actual criteria of the Wolff-Parkinson-White syndrome are: a short P–R interval and an abnormal but not necessarily prolonged QRS complex.

In view of this, and of the available histologic evidence of the existence of an aberrant A–V conduction pathway, it is suggested that the syndrome be known as the "*aberrant atrio-ventricular conduction*."

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THE SIGNIFICANCE OF THE PULMONARY DIASTOLIC MURMUR IN CASES OF MITRAL STENOSIS

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The origin of the soft-blowing diastolic murmur heard over the pulmonic area in patients with mitral stenosis has aroused considerable interest since the time of Graham Steell and Pawinski. No unity of view has been reached, although most authors consider the murmur as purely functional.

Graham Steell[23] in 1888 described "a murmur due to pulmonary regurgitation, such regurgitation occurring independently of disease or deformity of the valves, as the result of long-continued excess of blood pressure in the pulmonary artery." He defined it as a functional murmur very variable in intensity, now distinctly heard, at other times "indistinct or inaudible." A few years later Pawinski[15] described the same auscultatory phenomenon in patients with mitral stenosis and found at postmortem the signs of long-standing hypertension in the pulmonary artery. Since that time the soft diastolic murmur has been recognized as one of the occasional findings in mitral stenosis, and has been accepted as a functional murmur associated with extreme dilatation of the pulmonary artery and present during episodes of heart failure. It is, however, rarely heard. Cases have been reported by Vaquez and Magniel,[26] Ribierre,[18] Laubry and Thomas,[7] Scimone,[22] White,[27] Scherf,[20] Harvier and co-workers,[5] Schwartz,[21] and others. Postmortem findings, when available (as in 6 cases of Scherf[20] and 1 of White[27]), revealed dilatation of the pulmonary artery and undamaged pulmonic valves. Sussman and co-workers[24] described what they called a Graham Steell murmur in cases of Lutembacher's syndrome.

Case Reports. Case 1. *Mitral stenosis, pulmonic insufficiency.* John McS., a 23 year old white male, was first seen in May, 1942. One brother died of rheumatic heart disease and pneumonia. The patient had recurring episodes of joint pains during the previous 10 years, once accompanied by slight fever and lassitude, and during this period he occasionally raised blood-streaked sputum. Recently he had dyspnea and precordial distress, at times severe precordial pain radiating to the left arm.

Physical examination showed a tall, slender young man with severe cyanosis especially pronounced around the lips and the nose-tip, but no clubbing of the fingers or toes. The pulse was weak, small and completely irregular. The chest was deformed due to protrusion of the sternum and precordial area. Multiple pulsations were visible in many intercostal spaces and the epigastrium, particularly in the apical region. Palpation revealed a diastolic thrill over the apex and the mid-precordium, and by percussion, a rounded cardiac profile was outlined. Auscultation revealed the following signs: (1) A rumbling diastolic murmur (Grade 5) extending over an area from the 4th rib to the apex. (2) A soft blowing diastolic murmur (Grade 3) confined largely to the pulmonic valve area. (3) A short harsh systolic murmur over the xyphoid

process (Grade 2). (4) A more prolonged harsh systolic murmur (Grade 3) over the pulmonic area. (5) The second pulmonic sound was loud and snapping.

There were no peripheral signs of aortic insufficiency and the blood pressure was 140/90. There were no signs of congestive failure. The electrocardiogram showed auricular fibrillation and marked right axis deviation.

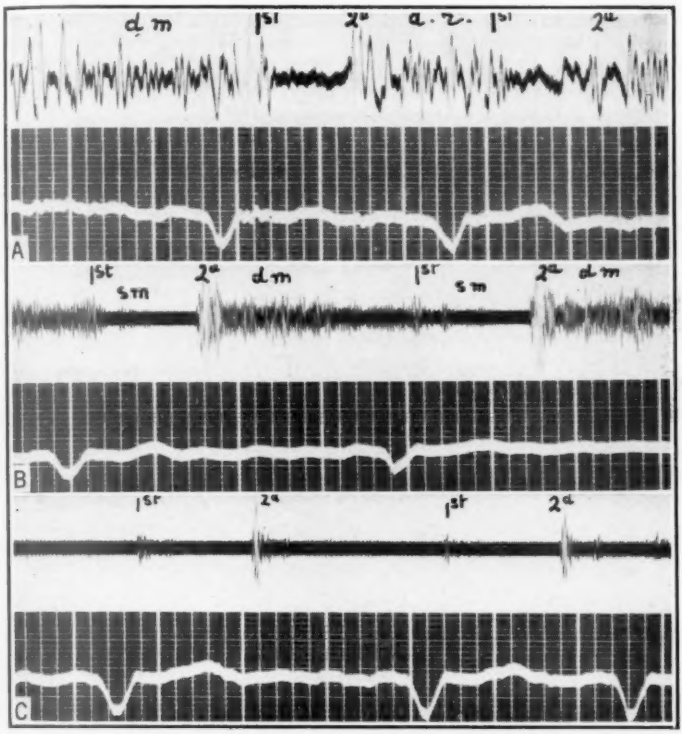

FIG. 1.—Case 1. *A*, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. *B*, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. *C*, Phonocardiogram recorded at the aortic area with logarithmic microphone; electrocardiogram.

There was slight secondary anemia, with normal white cell count and differential. The blood Wassermann and Hinton tests were negative. The urine was normal and had a specific gravity of 1.026. Oxygen saturation of the femoral arterial blood was 90%. Arm to tongue circulation time (decholin) was 44 seconds, and the arm to lung circulation time (ether) was 11 seconds. Roentgen ray examination disclosed a markedly enlarged heart, striking prominence of the pulmonary artery, a narrow aorta, dilatation of the left and right auricles and prominence and pulsation of the hilar vessels.

Phonocardiograms confirmed the auscultatory findings (Fig. 1). Of particular interest were the records obtained over the pulmonic and aortic areas showing a high-pitched diastolic pulmonic murmur with very slight transmission to the aortic valve area.

The pulmonic diastolic murmur was present at all examinations during a 2-year period of observation and showed a tendency to increase in intensity with the appearance of a diastolic thrill.

CASE 2. *Mitral stenosis, interauricular septal defect, pulmonic insufficiency.* Mary McD., a 49 year old white housewife was first seen in March, 1940, complaining of dizziness, palpitation and dyspepsia. At the age of 4 she had pertussis, at which time a diagnosis of heart disease was made. At the ages of 11 and 14 she had rheumatic fever, and 10 years later a mitral lesion was recognized for the first time. Shortness of breath was noted since the age of 11. Four years prior to examination she began to have nocturnal attacks of squeezing precordial pain. During the past 10 years dizziness, palpitation, intense sweating, swelling of the ankles and cough with bloody sputum occurred occasionally. More recently a severe attack of dizziness was followed by numbness of the right half of the body. She married at the age of 21 and had 15 pregnancies. Twelve of these were interrupted by abortion, 3 ended normally. The 3 children are in good health.

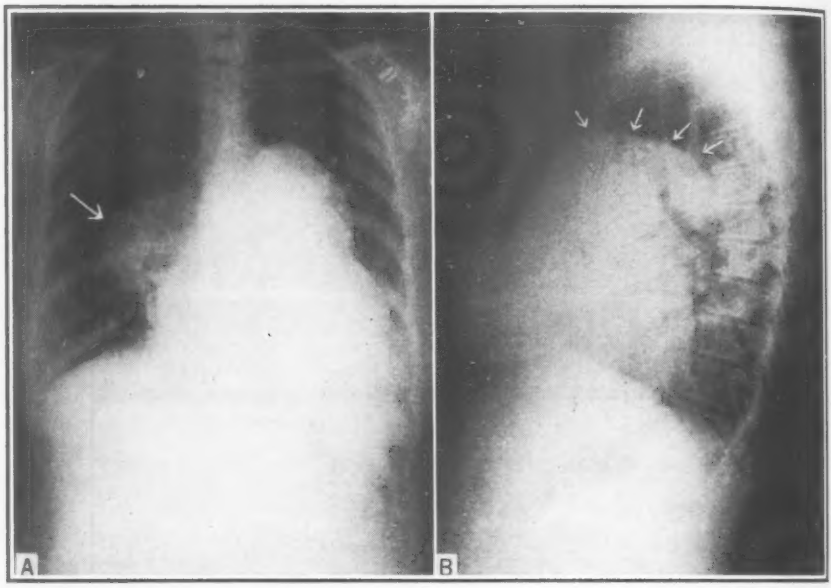

FIG. 2.—Case 2. Roentgen ray of the chest. *A*, Frontal view. The shadow in the right mid-lung field is a dilated branch of the pulmonary artery. *B*, Left anterior oblique, showing the dilated pulmonary artery and left branch.

Physical examination showed a strongly built woman, moderate cyanosis of the lips, without clubbing of the fingers or toes. The pulse was small and regular at a rate of 100. The right radial pulse seemed at times smaller than the left. There was intense pulsation of the external jugular veins and of the carotid arteries. A diastolic thrill was palpable over the apex. Percussion revealed marked cardiac enlargement. Auscultation disclosed a rumbling diastolic murmur at the apex and blowing systolic and diastolic murmurs in the second and third left interspaces. The latter murmurs were fairly well transmitted toward the left clavicle, but very poorly toward the right side and toward the suprasternal notch, and were inaudible over the carotids. The blood pressure was 134/84 and there were no peripheral signs of aortic insufficiency.

Laboratory studies showed normal blood cell counts and urine, and the blood Hinton and Wassermann tests were negative. Electrocardiogram showed normal sino-auricular rhythm, right axis deviation, and inverted or diphasic T waves in Leads I and II. Phonocardiograms confirmed the aus-

cultatory signs (Fig. 3). The arm to tongue circulation time (decholin) was 25 seconds. Roentgen ray examination revealed moderate enlargement of the right ventricle, but only slight dilatation of the left auricle, and a narrow aorta. The pulmonary conus was markedly prominent, measuring 5.6 cm. in diameter, and the pulmonary artery branches were markedly dilated on both sides; the hilar shadows on the right showed expansile pulsation (Fig. 2). There was no evidence of chronic pulmonary congestion.

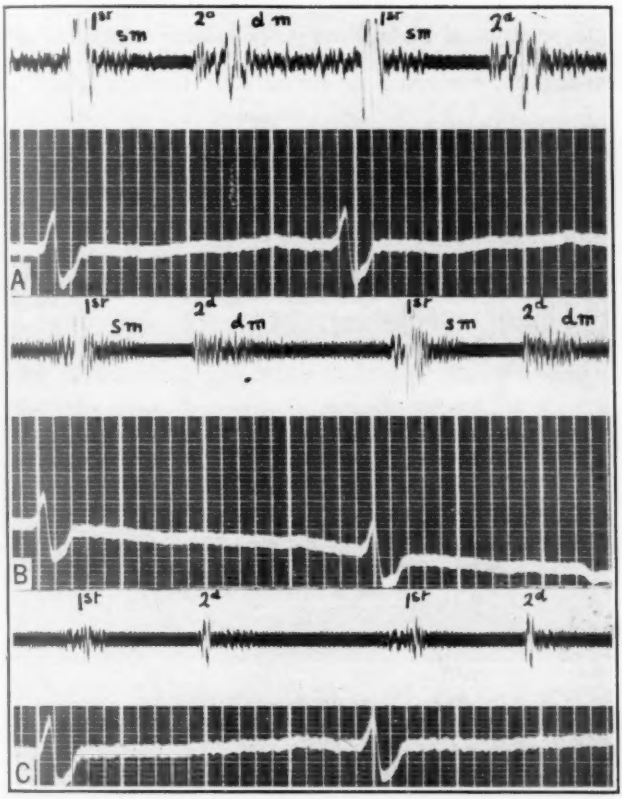

FIG. 3.—Case 2. *A*, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. *B*, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. *C*, Phonocardiogram recorded at the aortic area.

She was digitalized and thereafter edema of the ankles or other signs of congestive failure were absent. The cardiovascular signs remained unchanged at 15 subsequent examinations.

CASE 3. *Mitral stenosis, interauricular septal defect pulmonic insufficiency.* H. S., a 21 year old white male, was first seen in the Out-Patient Department of the Beth Israel Hospital in 1937. After an attack of scarlet fever 10 years previously, he was told that he had heart disease. Shortness of breath and precordial pain occurred with increasing severity in recent months. There was no history of rheumatic fever or joint pains.

Physical examination showed faint cyanosis of the lips, but no clubbing of the fingers or toes. The apex beat was visible in the 5th interspace, 11 cm. from the midsternal line and was diffuse. The right border of the heart was

3.5 cm. from the midsternal line. Systolic and diastolic thrills were palpable over the apex. A rough-blowing systolic murmur and a rough diastolic rumble were heard at the apex and a soft-blowing diastolic murmur in the 2nd left interspace. The latter was always present and increased in intensity during the following 11 years. No peripheral signs of aortic insufficiency were present. The pulse was 98, the blood pressure 120/70.

The blood counts, urine examination and blood Kahn and Hinton reactions were normal. Electrocardiogram showed a normal sinus rhythm, marked right axis deviation, diphasic T_2 and inverted T_3. P_1 was notched, P_3 was prominent. Roentgen ray examination showed enlargement of the right and left ventricles, a small aorta, aneurysmal dilatation of the pulmonary artery, but no dilatation of the left auricle.

Phonocardiograms confirmed the auscultatory findings (Fig. 4).

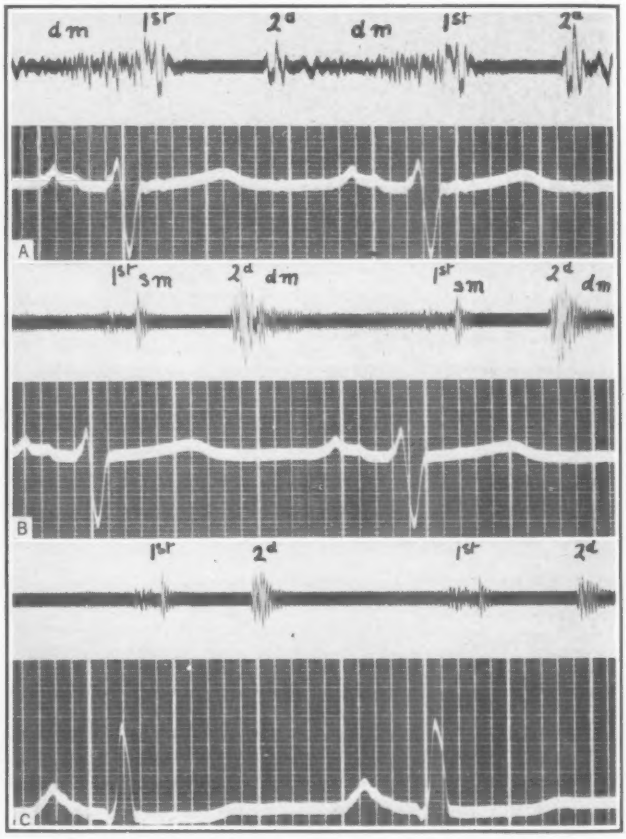

FIG. 4.—Case 3. *A*, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. *B*, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. *C*, Phonocardiogram recorded at the aortic area; electrocardiogram.

Discussion. To facilitate the differential diagnosis between aortic and pulmonic insufficiency, a table was constructed (Table 1) from the writings of several authors (Pezzi,[16,17] Schwartz,[21] Harvier *et al.*,[5] White,[27,28] Sussman *et al.*[24]). Applying these criteria to the cases here

reported we made a diagnosis of pulmonic insufficiency in each one. The signs remained essentially unchanged on repeated observations over a period of years. Two possibilities were considered as explanation for the pulmonic insufficiency:

(*a*) *Functional insufficiency of the pulmonary valve* (Graham Steell murmur) due to temporary dilatation of the pulmonary conus or artery associated with congestive failure.

TABLE 1.—MITRAL STENOSIS WITH AORTIC AND WITH PULMONARY INSUFFICIENCY

Sign	Mitral stenosis plus aortic insufficiency	Mitral stenosis plus pulmonary insufficiency
Cyanosis	Moderate	More intense
Axis deviation	Slight right axis deviation or no deviation	Marked right axis deviation
Pulse pressure	Ample	Small
Diastolic pressure	Low	Normal or high
Strong systolic pulsation (inspection, palpation, graphic tracing) with possible systolic thrill	Present over suprasternal notch and lateral cervical regions	Present over second left interspace
Systolic murmur (auscultation, phonocardiography)	Present over second right interspace, transmitted to suprasternal notch and to carotid arteries	Present over second left interspace transmitted toward left clavicle
Diastolic murmur	Radiating along left sternal border	Restricted to a small area
Size of pulmonary artery and of aorta (Roentgen ray)	Pulmonary artery either slightly dilated or normal; aorta either normal or dilated	Very marked dilation of pulmonary artery (resembling aspect of some congenital hearts); small aorta
Pulsations of pulmonary artery and of aortic arch (Roentgen ray; Roentgen-kymography)	Increased pulsation of aortic arch; normal pulsation of pulmonary arch	Small pulsation of aortic arch, very ample pulsation of pulmonary arch and of pulmonary branches
Hilus dance (fluoroscopy; Roentgen-kymography)	Absent	Present

(*b*) *Organic pulmonic insufficiency* due to inflammatory lesions of the valves or permanent dilatation of the pulmonary conus or artery.

The inconstancy of the murmur and its more common occurrence during congestive failure were emphasized by Graham Steell[23] and regarded as evidence of its functional origin. White[27] was of the same opinion. In Scherf's[20] cases the murmur was found only late in life and during congestive failure. Since in our cases the murmur was constantly present and independent of failure, a functional origin of the pulmonic insufficiency was considered an inadequate explanation.

Stretching of the pulmonary artery secondary to arteriosclerosis was regarded as the cause of pulmonic insufficiency by Laubry and Thomas,[7] Harvier *et al.*,[5] Scimone,[22] and others. In pulmonary arteriosclerosis unaccompanied by mitral stenosis, a pulmonic diastolic murmur occurs only in some of those cases in which there is also an *aneurysm of the pulmonary artery* (Arrillaga[2]). In interauricular septal defect with or without an associated mitral stenosis, marked dilatation of the pulmonary artery is usually present, but a pulmonic diastolic murmur occurs in only some of the cases (Abbott,[1] Lutembacher[10,11,12] Roesler,[19] Laubry and Thomas[7]). Even in cases of *aneurysm of the pulmonary artery due to syphilitic arteritis*, the murmur may be absent. In 2 cases observed by one of us (Luisada,[8,9]) one had no diastolic murmur, the

other only a very faint one. The conclusion follows that increased pulmonary pressure and arteriosclerosis and dilatation of the pulmonary artery do not always give rise to pulmonic insufficiency. An analogous situation exists in cases of arterial hypertension and arteriosclerosis of the aorta.

The studies of Gouley and Eiman,[4] von Glahn and Pappenheimer,[3] and Kugel and Epstein[6] indicate that lesions of the pulmonary artery and pulmonary valve may occur in rheumatic fever. Kugel and Epstein found rheumatic involvement of these structures in 17 out of 24 cases, 2 with gross changes in the pulmonary artery and 6 with verrucæ on the pulmonic valve. Microscopic study showed that 14 out of 24 cases had evidence of pulmonary valvulitis and in 3 of these Aschoff bodies were present. The most constant site of the arterial lesions was the insertion of the valves at the root of the pulmonary artery. These facts offer evidence to support the contention that the constant pulmonic insufficiency observed in our cases depends on deformity of the valves or permanent dilatation of the vascular structures, or both, and not on transient functional alterations secondary to congestive failure or fluctuations in pulmonary artery pressure.

Summary. 1. Three cases of mitral stenosis, 2 with associated interauricular septal defect, are described in which pulmonic insufficiency was constantly present and independent of congestive failure. None have died. Phonocardiographic records of the murmurs are included.

2. The clinical signs of pulmonary insufficiency and its differentiation from aortic insufficiency are reviewed from the literature and tabulated.

3. Pulmonary insufficiency is not always transient and functional in cases of mitral stenosis with or without interauricular septal defect, but may be permanent and organic as in the cases here reported. The nature of the possible organic changes is discussed.

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SPONTANEOUS MEDIASTINAL EMPHYSEMA WITH PNEUMOTHORAX SIMULATING ORGANIC HEART DISEASE

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In a paper dealing with the differential diagnosis of coronary occlusion, Hamman[3a] discussed 3 cases of interstitial emphysema of the lungs in which the pain was similar in type and distribution to that seen in coronary artery disease. In this and later publications[3b,c] he called attention of the medical profession to the clinical picture resulting from the spontaneous occurrence of mediastinal emphysema. In 1937, Scott[8] reported 2 cases of the syndrome and again called attention to the fact that the pain of mediastinal emphysema may simulate and must be differentiated from that of angina pectoris. Since then other investigators have mentioned the necessity of considering spontaneous mediastinal emphysema in the differential diagnosis of pain in the chest.

In spite of the increasing number of case reports of spontaneous mediastinal emphysema in the literature, they are still scarce enough to lead one to believe that the condition is rare. In the past 3 years the author has seen 8 cases of the syndrome in soldiers. In 6 of these a left-sided pneumothorax was demonstrated roentgenologically. It is the purpose of this paper to record the findings in 4 of these cases and to point out the similarity of the condition to organic heart disease.

Case Studies. Case 1. A white male, aged 38, was admitted to the Station Hospital on November 25, 1943, complaining of pain in the left chest. He dated the onset of his present illness to November 20, 1943, when he was awakened from sleep by a sudden, severe pain in the left parasternal region at the level of the third rib. This pain spread rapidly over the left chest anteriorly and extended to the interscapular region posteriorly. Associated with this pain he rapidly became short of breath. His respiratory distress was much ameliorated when he sat up. The pain gradually subsided so that by morning it had been replaced by a dull ache. In spite of this pain and moderate exertional dyspnea, the patient was able to do full duty until November 26, when he developed a pleuritic type of pain in the left axillary region. He gave a history of a dry, non-productive cough of 2 weeks' duration. In January and September, 1943 he had experienced 2 similar attacks of pain in the left chest which came on suddenly, did not radiate and were not associated with dyspnea. The first attacks lasted a week and the second, 3 days. The pain

was not as severe as that experienced during the present illness. The patient was examined at sick call both times but Roentgen rays were not taken.

Physical examination revealed a well-developed, adult male in no acute distress. There were no abnormalities of the head, eyes, ears, nose or throat. The trachea was not displaced. Respiratory excursions were markedly diminished on the left side of the chest. Tactile fremitus was diminished and the percussion note was hyperresonant over the entire left chest with extension of the hyperresonant sound to the full capacity of the pleural space. The breath sounds and voice sounds were absent over this side. The right border of cardiac dullness was percussed 6 cm. to the right of the midsternal line in the fourth interspace. The sounds were muffled, the rate was 68 per minute and the rhythm was regular. No murmurs were heard. Over the lower two-thirds of the sternum, there were audible high-pitched, crunching, crackling sounds during both systole and diastole. These sounds became louder in the upright position, especially in full inspiration. The arterial pressure was 106 mm. Hg systolic and 64 diastolic. There was no evidence of emphysema in the subcutaneous tissues of the neck or chest wall. The abdomen was soft and no organs or masses were felt.

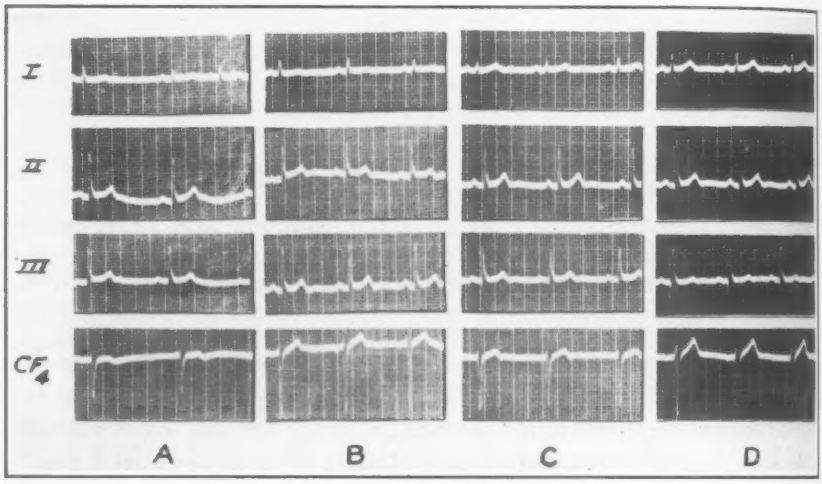

FIG. 1.—Case 1. Serial electrocardiagrams.

The patient's course in the hospital was afebrile and asymptomatic. Hamman's sign gradually decreased in intensity and finally disappeared on December 14, 1943.

Laboratory Data. Urine: acid, clear, specific gravity 1.014, no albumin or sugar, and an occasional epithelial cell and W.B.C. per high-power field. Blood: erythrocytes 3,900,000 per c.mm.; hemoglobin, 85% (Newcomer); leukocytes, 5400 with 61% neutrophils and 39% lymphocytes. The blood sedimentation rate (Westergren) was 17 mm. after 60 minutes.

Radiographic examination of the chest on November 24, 1943 revealed a 40% collapse of the left lung. There was an almost total collapse of the left upper lobe and a partial collapse of the left lower lobe. The mediastinal structures were shifted moderately to the right side. In the antero-posterior, oblique and lateral views no pneumomediastinum could be demonstrated. Examination on December 4 and December 12, 1943 revealed rapid reëxpansion of the left lung.

Electrocardiograms. The first electrocardiogram (Fig. 1*A*), taken on the day of admission, revealed a sinus mechanism with an occasional auricular

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extrasystole, a rate of 54 per minute, and a conduction time of 0.16 sec. Lead I shows a flat T wave less than 1 mm. in height. In Leads II and III, the S-T segments were slightly elevated. In the precordial lead, the initial upward deflection measured 0.5 mm. and the T wave was inverted.

An ECG (Fig. 1*B*) taken November 27, still revealed a flat T wave in Lead I and elevation of the S-T segments in Leads II and III. In the precordial lead, the initial upward deflection measured 2 mm. On December 7 (Fig. 1*C*) the T wave in Lead I was normal. The patient's normal ECG on December 15 (Fig. 1*D*) revealed a sinus mechanism, a rate of 66 per minute, and conduction time of 0.16 sec. The T waves were upright and normal in all leads and the initial upward deflection in the precordial lead measured 3 mm.

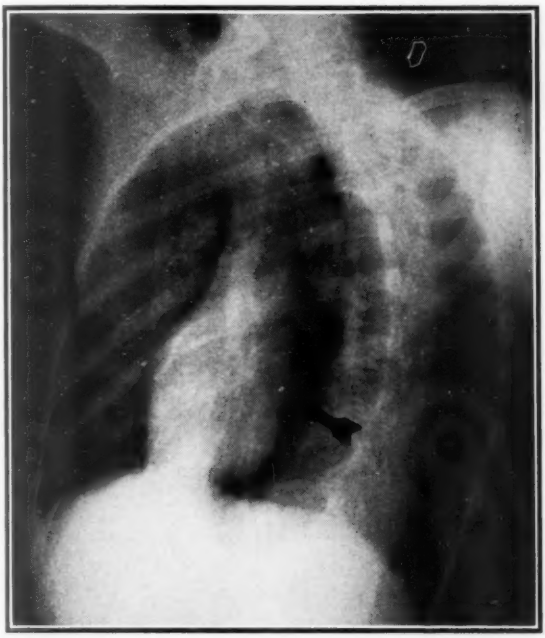

FIG. 2.—Case 2. Oblique roentgenogram illustrating air in the posterior mediastinum.

CASE 2. A white male, aged 23, was admitted to the station hospital on November 29, 1943, complaining of pain in the left chest. On the morning of admission, while doing calisthenics, he developed a sudden, sharp, knife-like pain under the left scapula. The pain extended over the left supraclavicular region to the anterior chest wall. Associated with this pain he became very dyspneic and was unable to take a deep breath. The pain and dyspnea persisted up to the time of admission to the hospital. He stated that he had a slight non-productive cough for the past few weeks and a head cold for the past 3 days.

Physical examination revealed a well developed young adult, moderately dyspneic but in no acute distress. The pharynx appeared granular and injected. The trachea was deviated to the right side of the midline. Respiratory excursions were decreased on the left side. The percussion note was hyperresonant, tactile fremitus, breath sounds, and vocal fremitus were diminished and no râles were heard on the involved side. The area of cardiac dullness was not elicited. The rhythm was regular, rate 72 per minute and no murmurs were heard. The arterial pressure was 130 mm. Hg systolic and 88 diastolic.

The patient was not seen again by the author until December 4, at which time the area of cardiac dullness was replaced by a hyperresonant percussion note and loud, crackling, crunching sounds in both systole and diastole were heard over the whole sternum. These sounds were much louder in full expiration.

The patient's course in the hospital was afebrile. He complained occasionally of mild substernal pains. Hamman's sign persisted until December 16. It varied in intensity and character. At times it had a clicking quality and at other times it was loud, crunching or popping. It was loudest in full expiration with the patient in the upright position and audible posteriorly between the spine and left scapula. The patient frequently heard the noise in his chest and described it as a "grinding sound."

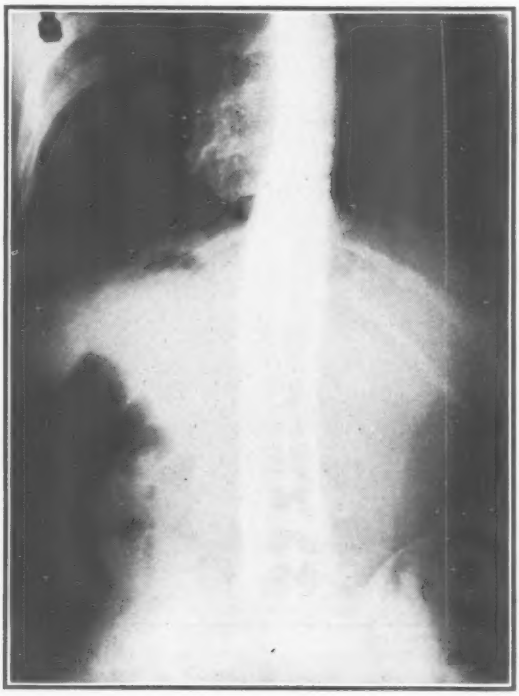

FIG. 3.—Case 2. Arrow points to air along the mediastinopleural reflexion of the left lung.

Laboratory Data. Urine: acid, clear, specific gravity 1.020, no albumin, sugar, cells or casts were found. Blood: erythrocytes 5,650,000 per c.mm.; hemoglobin 95% (Newcomer); leukocytes 5850 with 74% neutrophils, 24% lymphocytes and 2% eosinophils. The blood sedimentation rate (Westergren) was 7 mm. after 60 minutes.

Radiographic examination of the chest on November 29, 1943 revealed a pneumothorax in the left pleural cavity with approximately 50% collapse of the left upper lobe and 25% collapse of the left lower lobe. There was evidence of moderate dextro-rotatory scoliosis in the thoracic region with the apex of the curve at the level of the 7th dorsal vertebra. The anteroposterior, lateral and oblique views failed to reveal air in the mediastinal tissues. On December 6 (Fig. 2), radiographic examination revealed the presence of air in the posterior mediastinum. On December 9, a small amount of air was demonstrated in the mediastinal region along the upper portion of the left cardiac

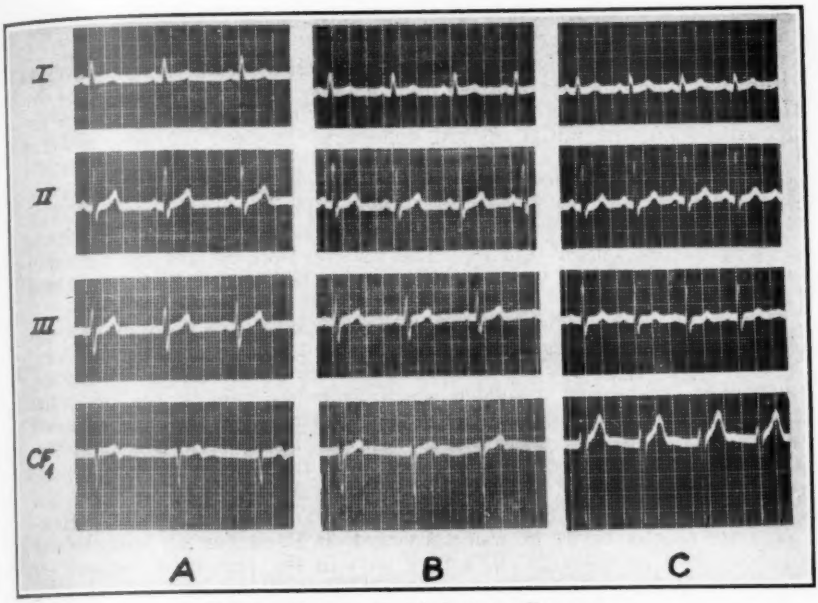

FIG. 4.—Case 2. Serial electrocardiograms.

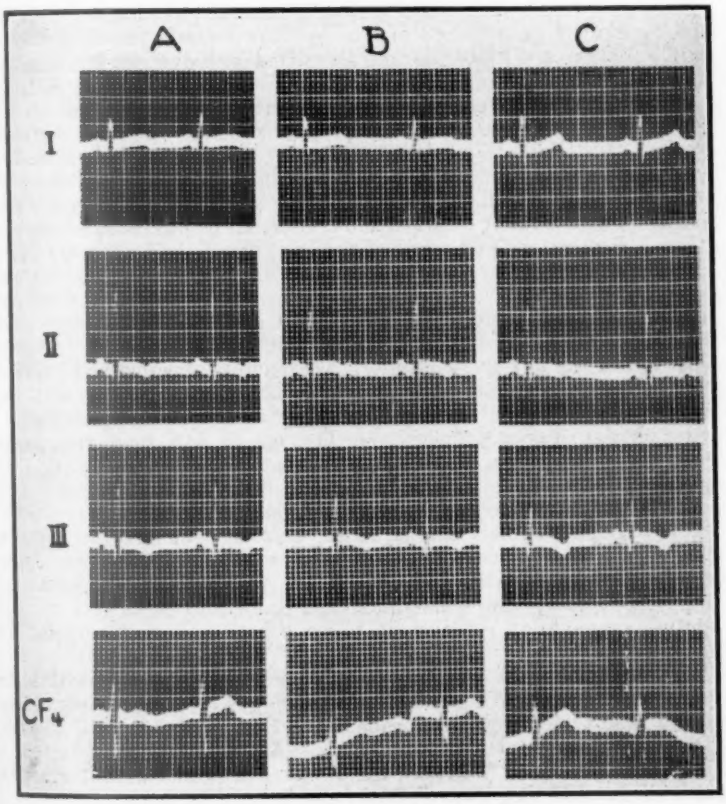

FIG. 5.—Case 3. Serial electrocardiograms.

contour and a small collection of air was noted along the mediastinopleural reflection of the left lung (Fig. 3).

Electrocardiograms. The first tracing (Fig. 4), taken on December 4, revealed a sinus mechanism, a rate of 66 per minute and a conduction time of 0.14 sec. The QRS complexes were slightly slurred and measured 0.08 sec. In the precordial lead, the initial upward deflection measured 0.5 mm. and the T wave was inverted. An ECG on December 10 (Fig. 4*B*) revealed no significant change, except in the precordial lead where the initial upward deflection measured 1 mm. and the T wave was upright. The patient's normal ECG on December 15 (Fig. 4*C*) revealed a sinus mechanism, a rate of 100 per minute and a conduction time of 0.14 sec. The T waves were upright and normal in all leads and the initial upward deflection in the precordial lead measured 3 mm.

CASE 3. A white soldier, aged 23, was admitted to the hospital on January 20, 1942, complaining of precordial pain and numbness of the left arm. On December 15, 1941 while instructing soldiers on the use of the mortar, the patient experienced a sudden sharp, knife-like pain in the precordial region associated with marked shortness of breath. The pain was increased by any attempt to take a full breath. He was admitted to a local station hospital shortly afterward. About 1 hour after the onset of precordial pain, while lying quietly in bed, he developed numbness and tingling down the medial aspect of his left arm. This lasted about an hour and then disappeared. However, until shortly before he was discharged on December 22, 1941, he was conscious of a persistent, dull, aching pain in the precordial region. On December 20, his temperature rose to 101° F. and rapidly subsided. His course in the hospital was otherwise uneventful. He felt perfectly well until January 19, 1942, when he overexerted himself helping to extinguish a brush fire. While returning to camp, after a swim in the river, he suddenly developed the same type of precordial pain which he had experienced a month previously. The pain was sharp and knife-like, and associated with dyspnea and numbness and tingling of the left arm. The patient continued to work, and that night the pain became more severe and was accentuated by lying on the left side. The next morning he was sent to the hospital for an ECG. Because of inverted T waves in Leads II and III of the ECG, he was admitted for further study.

Physical examination revealed a well-developed, young adult male who did not appear acutely ill. The head, eyes, ears, and nose were normal. The tonsils were moderately enlarged and cryptic but no pus could be expressed from them. Respiratory excursions of the left side of the chest were limited and the breath sounds and voice sounds were diminished over the left chest anteriorly and posteriorly. The area of cardiac dullness was not enlarged, the rhythm was regular, the rate 80 per minute and no murmurs were heard. The arterial pressure was 110 mm. Hg systolic and 62 diastolic. Over the lower portion of the left chest anteriorly were audible low-pitched "clicking, crackling sounds" in systole and diastole, which became louder with each inspiration. The abdomen was soft and no organs or masses were felt.

Hamman's sign was still present on January 21 and then disappeared. The patient's course in the hospital was uneventful and asymptomatic. The temperature on the day of admission rose to 99.2° F. and thereafter was normal. He was discharged on February 7, 1942.

Laboratory Data. Urine: amber, clear, acid, specific gravity 1.030, no albumin, sugar, casts or cells. Blood: erythrocytes 4,400,000 per c.mm.; hemoglobin 80%; leukocytes 6600 with 67% neutrophils, 2% eosinophils and 31% lymphocytes. The Wassermann and Kahn blood tests were negative. One sputum examination revealed no tubercle bacilli. The tuberculin skin test was negative.

An ECG on January 20 (Fig. 5*A*) revealed a sinus mechanism with a rate of 84 per minute and an A-V conduction time of 0.14 sec. The T waves were flattened in Lead I and inverted in Leads II and III. On January 22 (Fig. 5*B*), the T waves were normal in Lead I, diphasic in Lead II, and inverted in Lead III. On January 30 (Fig. 5*C*), the T waves in Lead I were increased in amplitude; in Lead II they were diphasic, and in Lead III inverted.

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Radiographic examination on January 20 revealed a slight compression of the left lung by pneumothorax. On January 27, the Roentgen ray revealed partial reëxpansion and, on February 2, complete reëxpansion of the lung.

CASE 4. A white soldier, aged 20, was admitted to the hospital on November 29, 1941 complaining of precordial pain. He dated the onset of his present illness to the afternoon of November 28, when he suddenly developed a sharp, stabbing pain in the left chest which radiated through to the back and up under the scapular region on the same side. He was slightly short of breath at the onset and could not take a deep breath. The severe pain persisted for about 1 hour and gradually subsided to a dull ache which was still present at the time of entry into the hospital. The admission diagnosis was "acute pericarditis." He gave no history of previous heart trouble, chest pain, dyspnea, cough, sputum, hemoptysis or weight loss.

Physical examination revealed a well developed, asthenic young male who did not appear acutely ill. The eyes, ears, nose, and throat were normal. There was no deviation of the trachea, and respiratory excursions were equal on both sides of the chest. The breath sounds and voice sounds were normally transmitted. The area of cardiac dullness was not enlarged, the heart sounds were normal, the rhythm regular, the rate 88 per minute, and no murmurs were heard. The arterial pressure was 130 mm. Hg systolic and 84 diastolic. The abdomen was soft and no organs or masses were felt.

On November 30, 1941 to-and-fro crepitations were heard to the left of the sternum over the apex of the heart. These were audible in systole and diastole during both phases of respiration, at times resembled a coarse pericardial friction rub and at other times were typical of Hamman's sign. These sounds were heard for three days and then disappeared. Except for a temperature of 99.2° F. on the day of admission, the patient's course in the hospital was afebrile. He was discharged January 17, 1942.

Laboratory Data. Urine: clear, acid, specific gravity 1.024 with no albumin, sugar, casts or cells. Blood: erythrocytes, 4,300,000 per c.mm.; hemoglobin, 75%; leukocytes, 7600 per c.mm. with 70% neutrophils, 13% eosinophils and 17% lymphocytes. A thick smear was negative for malarial parasites. The Wassermann and Kahn blood tests were negative. The blood sedimentation rate (Westergren) was 5, 3 and 3 mm. after 1 hour on 3 occasions. A stool examination was negative for ova and parasites. The tuberculin test was negative.

An ECG on November 29 revealed a sinus mechanism with a rate of 94 per minute and an A-V conduction time of 0.15 second. The QRS complexes measured 0.08 sec. and the T waves were upright and normal in all leads.

Radiographic examination on November 29 revealed a slight compression of the entire left lung by a pneumothorax with a small fluid level at the left base. The chest was otherwise clear. On December 9 the left lung was completely reëxpanded.

Discussion. The probable explanation of the genesis of spontaneous mediastinal emphysema is contained in the series of experiments by Macklin.[4] By overdistending a lobe of the lungs of cats and other animals, he was able to demonstrate that air enters the perivascular sheaths of the pulmonary vessels presumably through ruptures in the walls of the alveoli. The bubbles of air coalesce as they dissect along these artificial tunnels toward the root of the lung and eventually break through into the mediastinum. These air bubbles may form large blebs that actually impede the pulmonary circulation. Occasionally the air may extend from the perivascular sheaths into the adjoining connective tissue and dissect a path toward the pleura where it forms a subpleural bleb. From the mediastinum the air tends to follow with predilection the fascial planes, particularly the sheaths

surrounding blood-vessels. It may spread upward into the neck, axilla or over the chest wall. It may extend forward between the parietal pleura and pericardium to appear as blebs overlying the heart or downward into the retroperitoneal space.

Clinically, the spontaneous type of mediastinal emphysema is characterized by the sudden, frequently alarming development of precordial or substernal pain. The severity of the pain depends largely on the degree of distention of the mediastinal tissues by air. It may radiate to the back, shoulder, neck or down the left arm as it does in angina pectoris. There is frequently an associated pressure sensation under the sternum. The duration of pain is variable, lasting from several hours to several days. Dyspnea, cyanosis, and orthopnea may occur but are not characteristic of the syndrome. From this brief discussion it is evident that the type of pain associated with spontaneous mediastinal emphysema may simulate that of coronary thrombosis, pericarditis, dissecting aneurysm, pulmonary embolism, and mediastinitis. The differential diagnosis depends entirely on the clinical examination.

In mediastinal emphysema, air may be detected in the subcutaneous tissues of the neck and anterior chest wall. The area of cardiac dullness may be replaced by a hyperresonant percussion note. The pathognomonic sign of mediastinal emphysema is the peculiar sound heard over the precordium on stethoscopy. It has been described as crunching, crackling, popping, crepitant, and so on; changes in position and phase of respiration may alter the intensity and quality of the sound. It is synchronous with the heart beat, and may be heard during systole, diastole or both phases of the cardiac cycle. Pneumothorax has been present in some of the reported cases. In uncomplicated cases, there is no evidence of serious constitutional disturbance. The temperature as a rule is normal with normal or slightly elevated pulse and respiration. The blood pressure, white blood count, and sedimentation rate are usually within normal limits. The electrocardiograms, in cases where they have been reported, have failed to reveal any significant changes. Roentgenographic demonstration of air in the mediastinum is diagnostic.

A study of the foregoing case histories leads to the appreciation of the difficulty one may encounter in distinguishing spontaneous mediastinal emphysema with an associated pneumothorax from organic heart disease. The precordial pain, substernal pressure sensation, anginal type of radiation, dyspnea, similarity between Hamman's sign, and a pericardial friction rub, plus the abnormal ECG findings, may result in an incorrect interpretation of the underlying disease.

It is interesting to speculate on the cause of the anginal pain in Case 3 and in other cases that have been reported in the literature. There is little doubt that angina may occur in the absence of any pathologic lesion in the coronary arteries, and it is probable that gross disease of these vessels was not present, since most of the cases of mediastinal emphysema have been found in relatively young individuals. It seems reasonable to postulate the occurrence of a temporary

functional coronary insufficiency in these cases. This could be affected by one of several mechanisms. Right heart stasis, due to compression of the pulmonary blood-vessels by air in the vascular sheaths, may offer increased resistance to outflow of blood from the coronary vessels, *via* the Thebesian channels and coronary sinus, and lead to decreased coronary flow and myocardial anoxemia. Fisher[2] found dilatation of the right auricle and right ventricle at autopsy in a fatal case of spontaneous pulmonic interstitial and mediastinal emphysema occurring in a newborn infant. Microscopically, the large pulmonary vessels and their smaller ramifications were compressed and flattened by the air in the perivascular sheaths to such an extent as to seriously impede the blood flow through them. Experimentally, it has been demonstrated that an increased intramediastinal pressure has the same effects as increased intrapericardial pressure. If the tension reaches the level of the venous and intra-auricular pressure, the veins and auricles collapse and the circulation of blood stops. It is possible that the air also exerts direct pressure on the coronary vessels through both layers of the pericardium and even causes tamponade of the heart itself.

The demonstration of ECG changes in 3 of the cases is a point of particular interest. A review of the literature reveals no report of similar changes. Several investigators have indicated that mediastinal emphysema may simulate exactly the clinical picture of coronary thrombosis and suggest electrocardiography as an aid in the differential diagnosis of these two conditions. The few ECG studies that have been reported in mediastinal emphysema have revealed no significant abnormalities. Although not diagnostic, the serial ECG changes in our 3 cases, in the presence of clinical symptoms, could easily be mistaken for serious myocardial damage. It is likely that the associated pneumothorax produced these ECG abnormalities. Similar records have been noted in patients in whom a spontaneous pneumothorax simulated coronary disease;[1,9] and several investigators,[5,6,7] have noted that pneumothorax, probably by rotating the cardiac axis, may produce ECG changes suggesting coronary disease. These are most commonly T wave abnormalities, S-T deviation from the iso-electric level and absent or greatly reduced initial deflection in the standard Lead IV ECG.

The combination of pneumothorax with mediastinal emphysema in each of the 4 cases is worthy of comment in view of the obscure etiology of benign spontaneous pneumothorax. One of the most commonly accepted theories is that of a ruptured emphysematous bleb. In his experiments, Macklin was able to demonstrate the formation of such subpleural blebs. This followed the dissection of air out of the perivascular sheaths into the connective tissue and eventually to the pleura. More commonly the air reached the pleural cavity through a rent in the wall of the mediastinum. Experimentally, he found it easy to force air from the mediastinum into the pleural cavity, but not in the reverse direction. Hamman suggests that this mechanism of rupture of the air from the mediastinum into the pleural cavity

may explain the development of some cases of spontaneous pneumothorax better than the theory of ruptured subpleural bleb.

Ordinarily, the pneumothoraces associated with mediastinal emphysema are small and not detected until a roentgenogram of the chest is taken. In the cases being reported, they were large enough to be detected on physical examination. As in the cases previously described in the literature, the pneumothoraces were all on the left side, a fact which has as yet not been adequately explained.

In each of the cases a definite diagnosis was made by detection of the typical sounds (Hamman's sign) over the heart. These sounds may show great variation in intensity and quality during the course of the patient's illness and may last for several weeks. Although it has been stated that the typical sound of mediastinal emphysema is easily differentiated from a pericardial friction rub, the author has noted in 2 of his patients that as Hamman's sign became less marked, it tended to assume the characteristics of a rough pericardial friction rub. This was particularly marked in the prone position. As the patients assumed the upright position, the typical crackling, crunching sounds reappeared.

Summary. Spontaneous mediastinal emphysema is briefly discussed with a short review of the pertinent clinical and experimental literature. Four new cases of spontaneous mediastinal emphysema associated with left-sided pneumothorax are described in which the clinical history, physical or ECG examination simulated organic heart disease.

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A METHOD FOR MEASURING SMALL AMOUNTS OF WEIGHT LOSS IN MAN*†

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Since Sanctorius measured his own weight loss in 1614, there have been many publications of insensible weight loss. The methods used have been reviewed by Benedict and Root[1] and will not be discussed

* Aided by a grant from the Rockefeller Foundation.
† This is the fifth paper from this Laboratory of Tropical Physiology.

in detail again. The methods have varied considerably in sensitivity as well as practicability. Most of them have been sensitive to 100 gm. The method of Lombard[5] is quite sensitive; the weighted balance responds to 0.02 gm. and the unweighted balance to 0.002 gm. Changes in weight are recorded graphically on a drum by means of a lever which magnifies the movement of the balance 10 times. The apparatus is particularly useful for measuring variations over a very short period of time. The sensitivity of the apparatus reduces its practicability to some extent, especially in long-time experiments. The "silk scales" sensitive to 5 to 10 gm., and the Sauter balance, sensitive to 0.10 gm. used by Benedict and Root, have been employed for prolonged studies of weight loss.[4,6] In the study of insensible loss of weight in infants, suitable adaptations of the ordinary laboratory type chemical balances have been made. Day,[3] for instance, was able to weigh infants with an accuracy of 0.02 gm. with such a balance. These methods have certain disadvantages, however, under many experimental circumstances.

It is the purpose of this report to describe a balance applicable in measuring insensible changes in weight over very short or long periods of time. It can be used as a sensitive balance, that is, sensitive to at least 0.05 gm., or when such a sensitivity is not desired, as in prolonged studies, the sensitivity can be reduced to almost any desired level.

The Balance. The balance is illustrated by Figures 1 and 2. The balance as delivered by the manufacturer* consists of a heavy steel frame which supports the fulcra and arms above. The subject is suspended by the arm on the right and the weights are suspended by the arm on the left. The ratio of the lever lengths, or weight ratio, is 4:1. The scale as received from the manufacturer is not very simple to use and, therefore, certain modifications are necessary.

Figure 1 is a diagrammatic representation of the modified balance. The various parts are labeled in detail so as to simplify the interpretation of all figures. The balance is mounted as follows:

1. The *air dampers* are made on the principle of the air dampers of the Curie type of commercial chemical balance. These dampers are constructed as shown in insert *A*, Figure 1. They consist of a group of metal cylinders made of 26 gauge galvanized iron sheeting. The outer cylinder has a diameter of 14 inches, and the succeeding inner ones are made smaller, so that there is $\frac{3}{8}$ inch clearance between the walls of all of them. a'' and b'' (insert *A*) are cylinders which are entirely enclosed to form pistons. The set of cylinders labeled a' and b', and represented by the solid lines (insert *A*), are clamped to the upper and lower surfaces of the bottom shelf of the weight-bearing end of the balance. The outer group of cylinders labeled a and b (insert *A*) and represented by the interrupted line, are so arranged that they may be moved as necessary to avoid any friction between the inner group of cylinders when the weight-bearing end of the balance moves. The rigid arm (*C*) and wooden platform (a''') permit adjustments of the outer group of cylinders.

The dampers bring the balance to a standstill in 6 minutes instead of 23, once it has been set into maximum pendulous vibration.

Other forms of dampers, such as oil containing a paddle fixed to the fulcrum region of the balance, small electromagnets, and so on, were tried, but were found to produce errors or were too cumbersome or complicated.

2. *The Photographic and Recording Portions of the Balance.* To magnify the movements of the balance, to record them photographically for a permanent

* Buffalo Scale Company, Buffalo, N. Y.

record and to increase the accuracy, the following was constructed: An aluminum plate (*i*) was fixed to the beam of the balance near the main fulcrum and so arranged as to prevent any rubbing of parts when the balance vibrated. A hole was drilled and tapped into the aluminum plate and an aluminum rod ($\frac{1}{4}$ inch in diameter) screwed into it so that the center of the rod was in the center of the knife edge of the central fulcrum of the beam. The aluminum rod was long enough to extend 3 inches beyond the side frame of the balance. The distal end of the rod held a mirror (*o*) mounted as shown by insert *B*

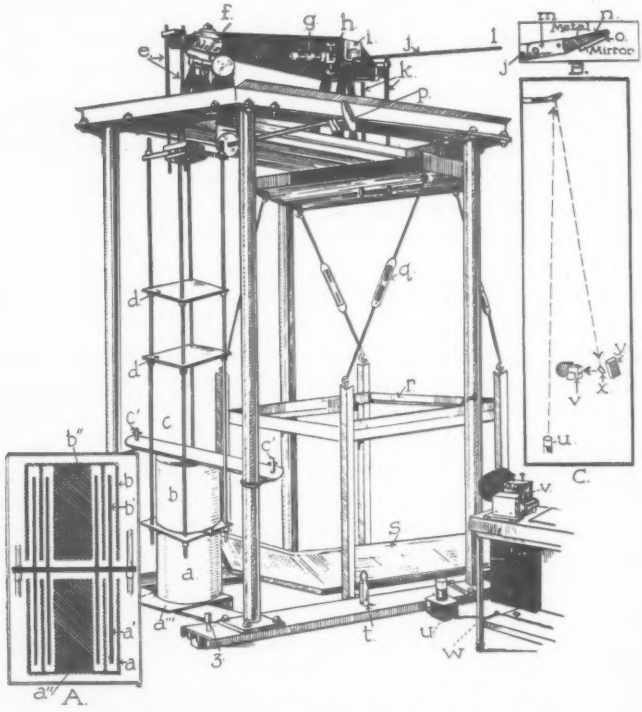

FIG. 1.—Diagrammatic representation of the balance.

A, Cross section of the *air dampers*; *a*, *b*, outer sets of air dampers; *a'*, *b'*, inner sets of air dampers; *c*, board supporting outer set of air dampers (*b*); *c'*, wing belts for adjusting air dampers (*b'*); *d*, plates for supporting counterweight for balancing subjects; *e*, rods suspending weight carriage; *f*, mirror for reading scale (Fig. 1) for gross adjustments of balance when adding weights; *g*, *h*, screw weights for setting balance for zero; *i*, plate added to balance to support rod (*j*); *j*, rod to support mirror.

B, Insert showing details of mirror cemented on end of rod (*j*); *k*, rods suspending frame for subjects; *l*, mirror mount (see insert *B*); *m*, metal segment which permits rotation of mirror (*o*) along transverse axis of rod (*l*); *o*, concave mirror (focal length 2 meters); *p*, arm for release of balance when weighing; *q*, screw for leveling subject in cot and frame; *r*, angle iron frame which may be used to support other apparatus used simultaneously with weighings; *s*, metal cot made of $\frac{1}{2}$ inch mesh wire and angle iron; *t*, locks (of which there are 4) used to steady subject's side of balance; *u*, lamp; *v*, camera; *w*, camera table; *x*, plane mirror; *y*, cover for mirror (*x*); *z*, screw for leveling scale.

C, Insert showing travel of light beam with camera slit for recording.

(Fig. 1). Aluminum joints (*m*) and (*n*) permitted adjustment of the mirror in any desired direction. The mirror is concave with a focal length of 2 meters. A 21 candle-power 6 volt lamp and housing (*u*) was mounted to the base of the balance near the floor (Figs. 1 and 2). An adjustable slit was made in the housing of the lamp and focussed onto the mirror (*o*). The image of the slit of light was then reflected by a plane mirror to an ordinary electrocardiographic type of camera. The mirror which reflects the light beam into the slit of the camera is mounted on the camera table and covered by a wooden box hinged so that the mirror can be uncovered when the camera is in use by rotating

the box. The top of the box covering the plane mirror is made of 24 gauge stainless steel sheeting with its two side borders turned over so that a sheet of ordinary typewriter paper can be slipped under these edges and held firmly

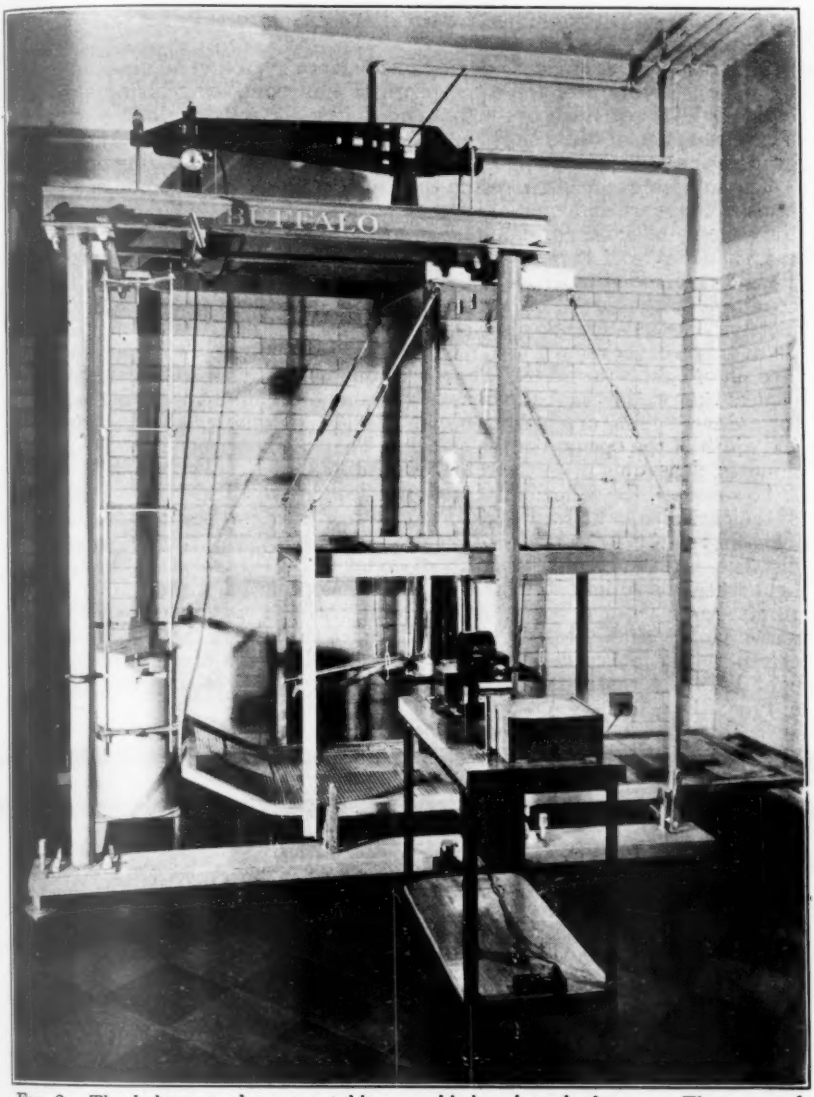

FIG. 2.—The balance and camera table assembled and ready for use. The parts of each are shown in Figure 1 and discussed in the text.

in place on top of the box. When the box is down covering the plane mirror, the light beam reflected from the concave mirror on the balance falls upon the paper on the top of the box, thus making it possible to follow the movement of the balance in a lighted room with a pencil. This is done whenever photographic recordings are not desired. The penciled records on the sheets of paper used on the top of the box may be kept as a permanent record.

An all-metal cot (*s*) (Figs. 1 and 2) was constructed of angle iron and $\frac{1}{4}$ inch mesh wire gauze. The cot is placed on the balance as indicated by the figures. Figure 2 shows a basal metabolism machine suspended on the balance so that the basal metabolism rate may be measured simultaneously with the weighing of the subjects. Similar types of large and heavy apparatus may be placed on the balance with the subject for simultaneous measurement of other physiologic processes.

3. *Method of Use of the Balance.* The balance is used in an air-conditioned room, the condition of the atmosphere of the room being maintained at a constant level several hours before and during the weighing of the subjects. The constancy of the conditions of the room prevents a condensation or evaporation of moisture upon, or from parts of the balance during use.

The subjects are made to rest in the supine position on the metal cot. Their arms and legs are abducted in order to facilitate evaporation of moisture from the skin of the axillæ, groin and genitalia. After the subjects have rested on the balance at least 15 minutes, the balance is unlocked and the beam released. Weights are added until the scale is balanced. When it is balanced, the air-condition unit is turned off and the air currents in the room stop almost completely. The balance is rechecked to make certain that it is in balance. The illumination of the room is then reduced so as not to interfere with photography. The slit of light is turned on. The reflected light beam is then reflected into the camera by rotating back the box on the camera table. A record is then made for a desired time, or not longer than it takes for the light beam to traverse the width of the opening in the camera. That requires from 15 to 30 or more minutes, depending upon the rate of weight loss.

To *calibrate*, the following procedure is employed: Just before completion of the recording, a known weight is added to the subject's side of the balance. This moves the light beam back into the opposite direction a measurable distance, a distance preferably about equal to that traveled by the beam of light when the subject lost his weight. It has been found that either 2, 5 or 10 gm. are necessary, 5 gm. usually being used. This is necessary for each measurement, as the sensitivity of the balance varies with the load. This type of calibration makes it possible to convert millimeters of movement of the light beam on the photographic record into weight loss in grams per unit of time.

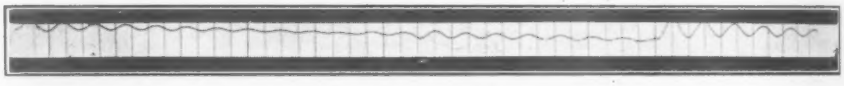

FIG. 3.—An original tracing.

The coarse smooth waves on the horizontal line produced by the light beam from the concave mirror on the balance represents slow pendulous vibrations of the balance due to slight movement by the subject. The very fine waves in the tracing seen on very close inspection are the movements in the balance produced by the respiration of the subject. The sudden rise in the tracing and large smooth waves seen at the terminal portion of the tracing were produced by the addition of 5 gm. to the subject's side of the balance on calibration. The vertical lines in the tracing are timer marks produced by the quarterly minute flashes of the timer light. Each fourth vertical line is darker than the others, thus marking the whole minute.

When prolonged experiments are conducted, such as 24 hour studies, the balance is employed more or less as an ordinary analytical balance, except that a series of weighings can be done with an accuracy of 0.050 gm.

Whenever a short or long study is conducted and a photographic recording is not desired, a penciled record may be made on the top of the box covering the plane mirror on the camera table. This was described in more detail with the description of the camera table and photographic technique (*vide supra*).

The rate of weight loss can be determined for a period as short as a fraction of a minute to any desired period of greater length.

Figure 3 shows a tracing which has been reduced about 10 times in size.

Accuracy of the Balance. In the next paper,[2] studies of weight loss were conducted over short periods of time, varying from 10 to 15 minutes. In order to determine the accuracy of the balance as used in these experiments, the following tests were conducted:

A burette containing mercury was placed upon the subject's side of the balance. The tip of the burette was drawn out to a fine capillary opening. The mercury was allowed to drop from the burette at a steady rate of flow and at a rate so that the weight of mercury lost over a period of 15 minutes was approximately the same as the rate of insensible weight loss found in preliminary experiments for normal subjects. A small beaker was suspended and held in place by a clamp under the burette so that the beaker and its support did not touch the balance. The balance was loaded with 150 pounds of steel blocks; that is, a weight equal to that of the average man. During the period of balancing the scale, the mercury was allowed to fall in a beaker placed on the scale under the burette. At the same time that a photographic recording of the change in weight of the balance was started, the previously weighed empty beaker, suspended and not touching the balance, was placed under the burette to catch the dropping mercury. After a period of about 15 minutes, while the recording was in progress, a 2 or a 5 gm. weight was dropped on the side of the balance supporting the burette in order to calibrate the recording as described above. The recording was then stopped simultaneously with the removal of the beaker collecting the mercury that escaped from the burette. By weighing the mercury caught in the beaker on an analytical balance, sensitive to 0.1 mg., the rate of weight loss due to the escape of mercury from the burette was accurately determined. The rate of weight loss was then determined from the photographic record. The balance was found to be accurate to ± 0.150 gm. per determination, or less than 0.050 gm. for the group of measurements.

Summary. The sensitive balance described above for the measurement of changes in weight has many advantages. It is accurate and sensitive. It can be used for prolonged studies, as well as short ones, even as short as a fraction of a minute. The use of photographic recording makes it possible to increase the accuracy and sensitivity of the determinations, as well as providing permanent records. The size of the balance provides for space for the placing of apparatus on the balance with the subjects so that other measurements can be carried out simultaneously with the weighings. It is possible to use the camera, by virtue of its construction, for recording other physiologic phenomena, such as blood pressure, simultaneously with the changes in weight. The nature of the assembly of the balance and photographic apparatus and the construction of the camera table renders the weighing almost automatic. Once the scale is balanced and the photography begun, the recording requires no attention except to place a weight on the subject's side of the balance for the purpose of calibration. The balance as used in the studies described in the succeeding paper

has an accuracy of ±0.150 gm. for an individual measurement, or 0.050 gm. for a series of measurements.

I wish to express my appreciation to Mr. G. Morgavi, Jr., for his valuable assistance in the development of the balance.

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THE RELATION OF TOTAL INSENSIBLE LOSS OF WEIGHT TO WATER LOSS FROM THE SKIN AND LUNGS OF HUMAN SUBJECTS IN A SUBTROPICAL CLIMATE*†

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The relationship of insensible water loss from the lungs to that lost from the skin has been studied very little. Many observers have studied the total insensible loss in weight, defined by Isenschmidt[7] by the following equation:

$$I.L. = I.W. + CO_2 - O_2$$

where I.L. represents the insensible loss of weight in grams; I.W. the grams of water vaporized, and CO_2 and O_2 the gaseous exchange in the lungs. I.W. may be further represented as follows:

$$I.W. = I.W._s + I.W._l$$

where $I.W._s$ represents the water in grams lost insensibly from the skin and $I.W._l$ that lost insensibly from the lungs. In the normal resting subject, I.W. represents about 93% of I.L.,[8] or the greater part of insensible weight loss is due to insensible water loss. Therefore, in the understanding of insensible weight loss, as well as insensible water loss, the relative values of the water lost insensibly from the lungs and the water lost insensibly from skin is of some importance.

Some observers have published studies conducted to measure such phenomena. Adachi and Ito[1] found their subject to lose 22.52 gm.

* Aided by a grant in aid from the Rockefeller Foundation.
† This is the sixth paper from this Laboratory of Tropical Physiology.

of water per hour insensibly from the skin, and 5.77 gm. per hour from the lungs when ordinary atmospheric air was inspired. Benedict and Benedict[2] found the water loss from the lungs to be 8.8 gm. to 12.05 gm. per hour, or about 40% of the total insensible water loss. The measurement of water loss from the lungs by Galeotti[6] conform to the results of these groups of observers.

During the course of studying insensible weight loss in subjects living in a subtropical climate, it was deemed advisable to separate insensible water loss from the lungs from that from the skin. The results, although not so different from those of others, were considered appropriate for description.

Methods and Materials. The experiments were conducted as follows: The total weight loss was measured on a special balance[3] which weighs a man with an accuracy of ±150 mg., or a series of subjects to an accuracy of 50 mg. The subject rested on a cot suspended from one arm of the balance. The cot was made of a metal screen and frame. Only metal parts were used on the entire balance. Weights were then added to the other arm of the balance. As the subject lost weight, the balance tilted. The degree of rotation was recorded on an electrocardiographic type of camera by a light beam reflected from a mirror properly arranged at the fulcrum of the balance. By means of a suitable timer and the beam of light reflected on the camera, the rate of water loss could be recorded photographically and measured accurately. A continuous recording of total weight loss for a 15 minute period was made for each subject. A Benedict-Roth type of basal metabolism machine was also suspended on the balance slightly above the patient on the patient's side of the balance. The water in the basal metabolism machine was replaced by a heavy mineral oil which was found not to change the weight of the machine by evaporation over periods as long as 24 hours. After recording the total weight loss for 10 to 15 minutes as described above, the B.M.R. machine was properly connected to the patient, filled with oxygen, the scale balanced and then the insensible loss in weight again recorded photographically as before. The change in weight recorded during the period of breathing in the B.M.R. machine represents changes mainly in water through the skin since there are no water or gaseous exchanges made between the lungs and the atmosphere during this time. Any weight lost during this time represents water vaporized from the body surface. The weight lost without the use of the B.M.R. machine minus the weight lost during the period when the B.M.R. machine was in use, was interpreted to represent the insensible weight lost through the lungs. As stated earlier in this paper, insensible weight lost through the lungs is about 93% vaporized water.

In most of the experiments, when the subjects were breathing in the B.M.R. machine, their metabolic rate was recorded on the recording drum.

In order to make certain that there was no change in weight due to: (1) the oil in the B.M.R. machine; (2) the ink used in recording the metabolic rate; (3) the paper used on the drum, or (4) the machine itself, the following experiments were conducted:

1. The scale was balanced with the B.M.R. machine with the oil and containing oxygen and ready for use without a patient on the scale. After 24 hours there was no change in weight.
2. Several pieces of the paper used for the metabolic recording were similarly balanced on the scale. After 24 hours there was no change in weight.
3. Recording paper was inked and then placed on the scale. No weight loss could be detected in 30 minutes.
4. A flat pan, 144 square inches in area, was filled with the heavy mineral oil used in the B.M.R. machine and placed in the scale. After 24 hours the pan did not change in weight.
5. In 7 experiments a "waterless" type of clinical B.M.R. machine was

used instead of the Benedict-Roth type. There was no difference noted in the results of the experiments. The "waterless" machine used was made only of metal and rubber, the bellows being rubber.

Each experiment was conducted as follows: After the room had been conditioned to a temperature of 75° F. ±1° and a relative humidity of 50% ±2%, the subjects were brought into the room and made to remove all their clothing, including jewelry. They then reclined in the supine position on the cot suspended from 1 arm of the balance. They were made to abduct their arms and legs so as to permit a more thorough evaporation of water from the axillæ and external genitalia. They were not permitted to rest the forearms and hands on the body; these were rested on the metal cot near to, but not touching the trunk. They rested at least 15 minutes. The forced air currents in the room were stopped by turning off the air-conditioning unit. The scale was blanced by adding the approximate amount of weight to the other arm of the scale. The loss in weight of the subject was recorded graphically as described above. The scale was "locked" and the air-conditioning unit was started again. During the period when the air-conditioning unit was stopped, the room temperature and relative humidity remained within the limits of variations described above. The subject readjusted himself and rested for another 10 to 15 minutes. He was then connected to the B.M.R. machine and a metabolic rate was determined while the loss in weight was recorded. In some instances the weight loss was measured first with the patient breathing in the B.M.R. machine and then with the patient breathing into the room.

When the weighings were made with the subject breathing into the B.M.R. machine, the volume of the B.M.R. machine decreased in volume equal to that of the O_2 consumed since the CO_2 expired by the patient was absorbed by soda lime. This decrease in volume of the B.M.R. machine produced a decrease in the buoyant force offered by the air of the room on the B.M.R. machine. This force is equal to the weight of a volume of room air equivalent to the volume of O_2 consumed during the study. During these weighings the change in buoyant force exerted by the atmosphere increased the weight of the B.M.R. machine. The necessary corrections for buoyance were, therefore, made for each observation.

In order to calibrate the scale so that the beam recorded photographically could be measured as weight loss in grams, the following procedure was followed in each experiment: At the end of the 15 minute period when the insensible weight loss was measured with the subject breathing into the room, a 5 gm. weight was gently dropped on the arm of the scale which suspended the subject. This deflected the light beam a variable amount, usually about 13 mm., varying of course with the weight of the subject. It was then very simple to convert millimeters of movement on the finished photographic tracing to grams of weight loss.

Twelve normal males varying in age from 21 to 33 years of age were studied. One was a Negro and the others white. They were medical students, technicians, and assistants around the laboratory. All of them were trained subjects, having been subjects for many other experiments. The studies were conducted in the afternoon and always more than 2 hours after a relatively small meal. No subject was permitted to drink within 1 hour of the experiment and none of them was thirsty at the time of the experiment. The experiment never lasted over 1 hour and no subject became tired or "restless" during the study.

In another group of studies, 4 subjects were enclosed in a tightly (tested by a water manometer) sealed metal cylindrical tank of 76 inches in length and 30 inches in diameter (Fig. 1). This tank was placed on the subject's side of the balance. The subject rested in the tank and breathed into the outside atmosphere by means of a B.M.R. type of rubber mouthpiece, which opened into the room air through the wall of the tank. The subjects were weighed for total loss in insensible weight before entering the metal cylinder and after being sealed in the cylinder. The conditions of the room air were the same as in the previous group of experiments.

Determinations were also made for the total insensible loss in weight in 10 normal young adult white males and Negro males. All of these subjects have lived in the South all of their lives. The measurement was made on the same days and under similar conditions for both groups of subjects.

The total insensible loss in weight was measured again in 10 normal young white males in the summer* and winter† months of New Orleans. The room conditions of the laboratory during both seasons were the same as described in the first group of studies.

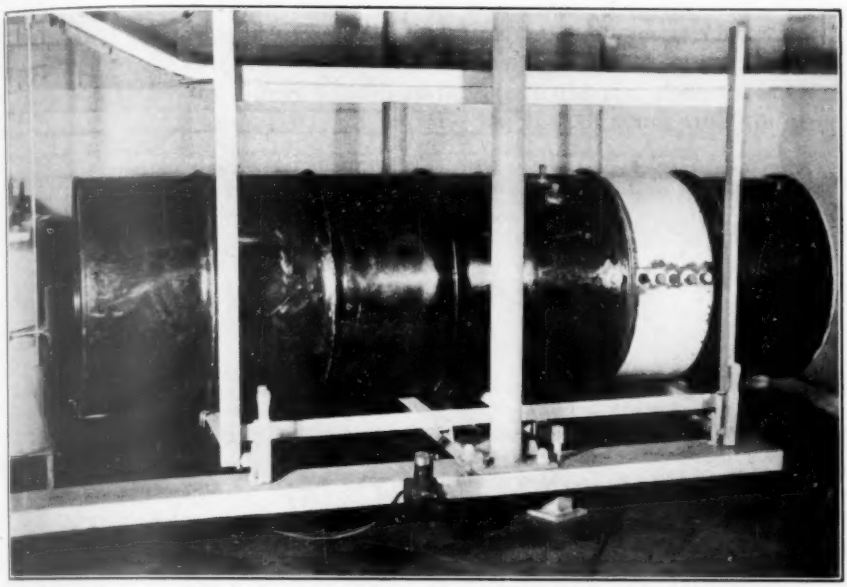

FIG. 1.—A long cylindrical metal tank in which the subjects were enclosed to control water loss through the skin while water loss through the lungs is measured. The photographic apparatus is not shown in place. The metal cot is shown on the balance above the tank. The subjects rested on this cot in order that the total insensible loss in weight could be measured.

Further studies were conducted on the bodies of 10 patients (see Table 5 for details) shortly after death. Only bodies without edema, skin abrasions or signs of dehydration or cachexia were used. The nose, eyelids, mouth, anus, vagina and urethra when opened were closed with sheets of rubber and cellulose tape. The bodies were placed on the balance and the rate of water loss through the skin measured as in the previous studies on living subjects.

In general it may be stated that in all studies the conduction of the observations, care of the subjects and the like, were essentially the same. All values of weight loss were expressed in grams per square meter of surface area per 10 minutes. The values were reduced to units of surface area‡ in order to correct for body size. Ten minutes were used as the unit of time, since the measurements were actually made over periods of about 10 minutes. The values can be easily converted to units of hours or days if necessary. Most of the subjects were studied several times and all living subjects were normal.

* During August, 1943 the mean temperature and relative humidity were 83.8° F. and 72.3%, respectively. The extremes were 74° and 96° F., and 50 and 100%, respectively.

† During February, 1943 the mean temperature was 57° F. and relative humidity 19.5%, with the extremes 30° and 79° F. and 36 and 100%, respectively.

‡ The surface area was calculated from the height and weight charts of Eugene DuBois and his associates.

Results. The results are summarized in Tables 1, 2, 3, 4 and 5. In the studies conducted on the 12 normal subjects on the balance with and without the use of the B.M.R. machine, the mean rate of total insensible loss in weight was found to be 3.42 gm. per square meter of body surface per 10 minutes,* with the extremes being 5.50 and 2.40. The mean rate of loss through the lungs was 1.79 and through the skin 1.63 (Table 1). The loss through the lungs was 52.23% of the total insensible loss, that is, with the subjects resting in a comfortable environment the weight lost insensibly through the lungs and through the skin is about equal. This relationship was also essentially true for each individual, as well as for the group, the values varying in absolute amounts but not relatively.

TABLE 1.—INSENSIBLE LOSS IN WEIGHT (GM./M²/10 MINUTES) FROM THE SKIN AND LUNGS OF 12 NORMAL ADULT MALES, AGES 23 AND 24, AND ONE 28

Subject No.	Room Temp. (° C.)	Room R.H. (%)	Total loss	Skin loss	Lung loss
1	23.6	22	3.073	1.708	1.221
2	23.6	43	2.651	1.778	0.873
3	23.6	44	5.503	2.753	2.850
4	22.5	30	4.615	1.746	2.869
5	23.6	46	2.396	0.955	1.441
6	23.6	39	3.045	1.396	1.649
7	23.6	48	2.720	1.690	1.030
8	23.6	55	3.066	1.050	2.016
9	24.6	30	3.226	1.674	1.552
10	23.6	46	2.868	1.310	1.558
11	23.6	55	4.564	1.880	2.684
12	23.6	55	3.335	1.660	1.675
Mean	..	..	3.418	1.633	1.785
Max.	..	..	5.503	2.753	2.869
Min.	..	..	2.396	0.955	0.873

Per cent of total lost from lungs, 52.23

TABLE 2.—INSENSIBLE LOSS IN WEIGHT (GM./M²/10 MINUTES) IN 4 NORMAL WHITE ADULTS
(Subjects placed in metal tank to isolate skin)

Subject No.	Total loss	Skin loss	Lung loss
1	2.724	0.600	2.124
2	3.463	1.741	1.722
3	3.038	1.338	1.700
4	1.783	0.668	1.015
Mean	2.497	1.087	1.665
Max.	3.463	1.741	2.124
Min	1.783	0.600	1.015

When the subjects were placed in a metal tank so as to control the water loss through the skin, while permitting the loss through the lungs to vary, the results were essentially the same as in the above group of studies (Tables 1 and 2) in which the B.M.R. machine was used to control weight loss through the lungs while weight loss occurred through the skin. There was a tendency for the insensible loss in weight through the lungs to be greater when the tank was used. The

* Henceforth, for the sake of brevity the unit of measurement will not be repeated since it is the same throughout.

loss through the lungs was 66.6% of the total insensible loss in weight, a difference of 14.4% over the first group of studies.

TABLE 3.—RATE OF INSENSIBLE LOSS OF WEIGHT IN 10 YOUNG NORMAL WHITE AND 10 YOUNG NORMAL NEGRO MALES

(The temperature and relative humidity of the observation room were 82° ± 1° F. and 60% ± 2% respectively)

White					Negro				
Subject No.	Age	Wt. (lbs.)	Surface area (m^2)	Weight loss (gm/m^2/10 min.)	Subject No.	Age	Wt. (lbs.)	Surface area (m^2)	Weight loss ($gm./m^2$/(10 min.)
1	32	160	1.93	2.282	11	30	127	1.61	3.798
2	22	135	1.76	5.294	12	25	131	1.68	2.069
3	25	178	1.98	7.234	13	20	146	1.69	3.582
4	24	160	1.88	3.612	14	26	145	1.81	3.257
5	24	160	1.85	3.496	15	30	175	1.97	4.144
6	25	156	1.85	1.988	16	38	173	1.95	5.467
7	25	155	1.87	2.934	17	18	118	1.60	1.734
8	23	155	1.88	2.176	18	41	186	2.01	2.579
9	23	130	1.70	3.084	19	32	135	1.73	3.617
10	26	160	1.80	5.019	20	16	140	1.72	5.575
Mean	..	..	..	3.483	Mean	..	..	..	3.582
Max.	..	..	..	7.234	Max.	..	..	..	5.575
Min.	..	..	..	1.988	Min.	..	..	..	1.734

TABLE 4.—COMPARATIVE RATE OF INSENSIBLE LOSS OF WEIGHT IN NORMAL YOUNG WHITE MALES DURING THE SUMMER AND WINTER MONTHS

(The temperature and relative humidity of the observation room were 75° ± 1° F. and 50% ± 2% respectively)

Subject No.	Age	Wt. (lbs.)	Surface area (m^2)	Total insensible weight loss ($gm./m^2$/10 min.)	
				Summer	Winter
10	26	160	1.80	5.218	4.287
21	29	190	2.02	2.442	2.407
22	22	185	2.07	2.994	3.756
23	33	159	1.88	2.986	3.860
24	22	155	1.82	2.921	4.523
25	33	170	1.97	2.529	3.184
26	24	135	1.68	3.570	3.470
27	28	180	1.98	2.549	3.045
28	23	175	1.94	2.294	3.188
29	24	185	2.06	3.548	7.357
Mean	..	..	..	3.105	3.908
Max.	..	..	..	5.218	7.357
Min.	..	..	..	2.294	2.407

The mean rate of total insensible loss in weight in the 10 young white and Negro male adults from the South measured under comparable conditions was 3.48 and 3.59, respectively (Table 3), there being no significant difference. Except for 1 instance (white subject No. 3, Table 3) there was no real difference from individual to individual. In this 1 subject the total insensible loss was over twice that for any individual in the entire group.

The mean rate of total insensible loss in weight in 10 subjects studied under similar laboratory environmental conditions was slightly greater during a cool winter month than a hot summer month, the values being 3.91 and 3.11, respectively. This was true for each individual considered separately except two (Table 4).

The mean rate of water loss through the skin of 10 bodies studied shortly after death was 0.92 (Table 5). The variations were 0.39 and 1.51; the statistical constants are shown in Table 5.

TABLE 5.—LOSS IN WEIGHT (GM./M²/10 MINUTES) THROUGH THE SKIN SHORTLY AFTER DEATH FOR ENTIRE BODY

Subject No.	Age	Sex	Color	Room Temp. (° C.)	Room R.H. (%)	Hours after death	Weight loss
30	47	M	W	27.2	35	3.5	1.51
31	49	M	C	27.2	35	2.5	0.87
32	50	F	C	27.2	37	3.3	0.95
33	54	F	C	27.4	50	2.5	0.39
34	59	M	W	25.5	64	2.0	0.71
35	33	M	C	25.5	36	3.8	1.00
36	51	F	W	25.5	52	3.6	0.75
37	26	M	C	25.5	78	6.0	0.93
38	62	M	C	25.5	78	1.3	1.25
39	18	M	W	24.0	50	4.0	0.85
Mean							0.92
Max.							1.51
Min.							0.39
Standard error of mean							0.095
Standard deviation							0.302
Standard error of standard deviation							0.068
Coefficient of variation							32.83%
Standard error of coefficient of variation							7.34%

Discussion. These experiments were designed primarily to give some insight into the factors making up I.W. and to establish normal values for the subtropical climate of New Orleans. The results were essentially the same as reported by others for different localities,[1,2,8] the main difference being the proportions of water lost through the lungs and skin. In general, less than 30% of the water vapor eliminated insensibly had been estimated to come from the lungs. Adachi and Ito[1] found a loss of 22.52 gm. per hour from the skin and 5.77 from the lungs when ordinarily atmospheric air was breathed. Benedict and Benedict[2] found the loss from the lungs to be about 40% of the total insensible loss. Galeotti[6] published measurements which conform with the latter report. Table 1 shows that our findings agree closely with the latter 2 groups of studies.

When the water loss from the skin was controlled by enclosing the subjects in a tightly sealed metal tank while they were allowed to breathe through an opening in the wall of the tank, the water loss through the lungs was slightly greater than when a B.M.R. machine was used to control water lost through the lungs. Such a difference might be accounted for on the basis of psychic influences on respiration, since the subjects appeared to breathe a little more deeply and rapidly when they were in the metal tank than when on the cot outside the tank. Although all subjects were trained, and repeated measurements were made, they commented on their consciousness of breathing when in the tank. There was very little, if any, rebreathing during the measurements made with the subjects enclosed in the tank, since the length of the tubing including the rubber mouth-piece was only 1 inch in length.

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The finding of a similar rate of loss in total insensible weight in the Negro and white subjects is in agreement with the studies of Robinson, Dill, Wilson, and Nielsen.[9] Any racial differences in adaptation to humid heat must be explained by other factors than racial differences due to the dissipation of heat by insensible perspiration.

The greater total insensible water loss in the winter than in the summer months in New Orleans is difficult to explain. Although the environmental conditions of the laboratory were the same during both seasons, the subjects who entered the laboratory during the summer commented upon the coolness of the laboratory. The laboratory was kept at a temperature of 75° F. and the outside temperature was usually in the 90's. In the winter the subjects always found the laboratory warm. At that time the outside temperature was in the 50's or lower, while the laboratory temperature was 75° F. It is possible that a sudden change in the temperature upon entering the laboratory could produce vasoconstrictions in the skin and lungs which might reduce the rate of water loss in the summer. The reverse effects would theoretically be true in the winter. It is also possible that these sudden changes in the conditions of the environment influenced the volume of the tidal air. It has been found[5] that the volume of tidal air increases markedly when a subject is moved from a cool and dry atmosphere to a hot and humid one, and the reverse effect is noted when he is moved from a hot and humid atmosphere into a cool one. It is possible that during the summer the volume of tidal air was decreased when the subjects left a humid and hot environment to enter the relatively cool and dry air-conditioned laboratory. It is unlikely that these differences are due to changes in metabolic rate, as it tends to change very little if at all in tropical climates at least.[10]

The rate of water loss through the bodies shortly after death averaged 0.92. This was water lost entirely through the skin. The mean value for living skin was 1.63. Such a difference might be due to an additional loss through the skin of living subjects by slow imperceptible sweating which was probably absent in the dead bodies. Studies on isolated areas of skin carried out in this laboratory,[4] however, showed that the rate of water loss through dead and living skin (with the subjects resting quietly in a comfortable room) maintained at the same temperature was essentially equal. When the temperature of the skin was lowered, the rate of water loss decreased more or less directly proportional to the change in temperature. In the present studies the skin of the living subjects was at a higher temperature than that of the dead bodies, the temperature of the skin of the latter being about atmospheric. Since most of the water lost through the skin under the conditions of the above experiments was lost by diffusion,[4] most of these differences in water loss through the skin of the living and dead bodies can be accounted for upon the basis of the differences in the effects of skin temperature upon the rate of diffusion.

It is well to emphasize that the above measurements show the skin to be an effective barrier to the loss of water from the body. This has

been indicated previously[4,11] for isolated small areas of dead and living skin. It was found that the skin is a very efficient inhibitor to diffusion of water from the body. The corneum was found to be the layer endowed with the greatest ability to inhibit loss of water by diffusion.[11]

Summary. The mean rate of total insensible loss in weight for 12 normal young white adult males living in the subtropical climate of New Orleans was found to be 3.42 gm. per square meter of surface area per 10 minutes. The mean rate of insensible weight loss through the skin was 1.63 and through the lungs 1.79. The latter represents 52.2% of the total insensible loss in weight. The values conform essentially with those reported by other observers for different areas of the world.

The mean rate of total insensible weight loss was found to be the same for 10 young white and 10 young Negro normal adult males. Any differences in the adaptability of the two races to hot and humid environments must not be related to cooling by insensible perspiration.

In 10 normal young white adult males, the mean rate of total insensible weight loss was definitely greater during the cool month of February in New Orleans than the hot humid month of August. Possible explanations for these seasonal variations are offered.

The insensible water loss through the skin of 10 dead bodies studied shortly after death showed a mean rate of loss in weight of 0.92. This is considered to be mainly loss by diffusion through the skin. The lower temperature of the skin of the dead bodies most probably explains the slower rate of loss of water through the skin of the dead bodies than that through the skin of the living ones.

The skin is an efficient inhibitor of the loss of water by diffusion.

We wish to express our appreciation to Mr. G. Morgavi for his keen interest in and contributions to these studies.

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USE OF POSTERIOR PITUITARY EXTRACT IN TESTS OF URINARY CONCENTRATION

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Measurement of the maximal ability of the kidneys to concentrate urine has long been recognized as a most valuable clinical estimate of renal efficiency. Its worth has not been reflected in sufficiently wide application. One reason for its relatively infrequent use is that it requires restriction of fluid or controls of food and fluid for 12 to 72 hours, which impose discomfort on patients. In an effort to circumvent these disadvantages Brunn,[4] (1921) Sodeman and Engelhardt[11] (1941), and Wall[14] (1943) administered subcutaneously posterior pituitary extract with the hope that its antidiuretic action would stimulate maximal urinary concentration during the succeeding short period. Their results were encouraging. However, substitutes for a procedure which has repeatedly demonstrated its accuracy and usefulness must be carefully evaluated before they are introduced into general usage. Our study was designed to compare the merits of the Addis test of urinary concentrating power with those in which pituitary extract was injected with or without periods of fluid deprivation.

Methods. Four series of concentration tests were made on 33 normal and 65 abnormal subjects. The abnormal persons were suffering from essential or malignant hypertension, chronic glomerular nephritis, or chronic pyelonephritis. The measurements of specific gravity were made with the Westphal-Van Slyke balance. The temperature of all specimens was adjusted to 20° C. and corrected for protein content (Alving and Van Slyke,[2] 1934). Where the samples were too small for this method, the determination was made pyknometrically.

The first test used was that devised by Addis[1] (1926). In it fluid is restricted for 24 hours. The specific gravity of the urine sample collected during the second 12-hour period was measured.

In a second series, 19 normal and 12 abnormal persons received 10 units of surgical pituitrin subcutaneously, and the test was conducted in a manner described by Sodeman and Engelhardt[12] (1942). The bladder was emptied, and urine was collected every 30 minutes for 3 hours. The specific gravity was measured with pyknometers of 2 ml. content.

As will be shown in Table 1, this test does not result in as great concentration as that in which fluid is withdrawn for 24 hours. Attempts were therefore made to combine short periods of fluid restriction with the antidiuretic principle of pituitary extracts. Since Stephens[13] had shown that aqueous solutions of pituitary extracts induce maximal antidiuresis only for 4 hours or less, the use of surgical pituitrin was discontinued. Greene and January[6,7] (1940) and Stephens[13] (1940) demonstrated that pitressin suspended in oil resulted in more marked and prolonged (12 to 36 hours) antidiuresis than aqueous solutions of pituitary extracts in both patients and animals with diabetes insipidus. Therefore, pitressin tannate in oil was used in the succeeding experiments.

In the first of these, 8 normal and 11 abnormal persons were given subcutaneous injections of 0.5 cc. of pitressin tannate in oil. The bladder was emptied immediately after the injection and no fluid was taken for 5 hours. The specific gravity of the urine formed during this period was measured. The results fell short of the standards established during the Addis examination. Therefore, the period without fluids was increased to 12 hours in 47 abnormal and 15 normal subjects, pitressin tannate in oil being given as before. As a control of this last procedure, the same subjects collected urine during a period of 12 hours in which no fluid was allowed. The mean and range of specific gravities resulting from these tests were calculated and the standard errors of the means were found after the method described by Bradford Hill.[9]

Comparison of urinary output during pituitrin antidiuresis and water deprivation was made for similar periods. Ten patients were given subcutaneous injections of 0.5 cc. of surgical pituitrin at 4-hour intervals during a 12-hour period. The bladder was emptied at the beginning of the test, and all urine formed was collected. The volume and specific gravity of these specimens were compared with those of the Addis tests performed on the same subjects.

TABLE 1.—NORMAL SUBJECTS

Test used	No. of subjects	Mean max. specific gravity	Lowest specific gravity	Highest specific gravity	Standard error of the mean
Addis fluid restricted 24 hrs.	32	1.0302	1.026	1.032	±0.000393
Sodeman and Engelhardt max. specific gravity during 3 hrs. following injection of pituitrin	23	1.0251	1.015	1.033	±0.00115
0.5 cc. pitressin in oil plus 5 hrs. dehydration	8	1.019	1.016	1.036	
0.5 cc. pitressin in oil plus 12 hrs. dehydration	15	1.0242	1.012	1.030	
12 hrs. dehydration	12	1.020	1.009	1.029	

In this and succeeding tables, standard error of the mean was calculated after the method of Bradford Hill[9] in those groups large enough to make such determinations significant.

TABLE 2.—ABNORMAL SUBJECTS

	Test Used			
	Sodeman and Engelhardt max. reading during 3 hrs. following injection of pituitrin	0.5 cc. pitressin in oil plus 5 hrs. dehydration	0.5 cc. pitressin in oil plus 12 hrs. dehydration	12 hrs. dehydration
Subjects	18	11	47	30
Mean max. specific gravity	1.0182	1.015	1.0181	1.0172
Lowest specific gravity	1.0115	1.008	1.008	1.006
Highest specific gravity	1.0225	1.023	1.028	1.033
Standard error of the mean	±0.00081	..	±0.00068	±0.0011
Addis test for comparison:				
Mean specific gravity	1.0201	1.016	1.0194	1.0202
Lowest specific gravity	1.014	1.008	1.009	1.015
Highest specific gravity	1.025	1.025	1.026	1.025
Standard error of the mean	±0.00063	..	±0.00061	±0.000607
Cases with difference of 0.003+				
Addis test greater	7	3	19	16
Substitute greater	1	0	4	4

Results. Tables 1 and 2 compare the results of the 4 tests of ability of the kidneys to concentrate urine to that of the Addis test. These tests consisted of: (1) injection of 10 units of surgical pituitrin, (2) injection of 0.5 cc. of pitressin tannate in oil followed by 5 hours of fluid deprivation, (3) injection of 0.5 cc. of pitressin tannate in oil followed by 12 hours of fluid deprivation, and (4) 12 hours of fluid deprivation. Table 3 compares the output and specific gravities of urine formed by 12 patients during each of two 12-hour periods of antidiuresis: (1) that induced by water deprivation of the Addis test, and (2) that induced by subcutaneous injections of 0.5 cc. of surgical pituitrin every 4 hours.

Among the normal subjects the differences among the various tests were striking. In the first in which surgical pituitrin was given

without fluid restriction the mean specific gravity was 1.025 as compared to the mean of 1.030 in the Addis test. These averages do not reflect the irregular pattern of results, since the range following pituitrin injections was 1.015 and 1.033 and the standard error of the mean ±0.0011, while the range was 1.026 to 1.032 in the control Addis examinations and the standard error of the mean only ±0.00039.

Five hours of fluid deprivation combined with injection of pitressin in oil yielded urine samples, the mean specific gravity of which was 1.019 with a range of 1.016 to 1.036. The mean value following 12 hours fluid deprivation and pitressin tannate was 1.024, and the range 1.012 to 1.030. Fluid starvation alone (12 hours) yielded urine samples with mean specific gravity of 1.020, and the range 1.009 to 1.029.

The same 4 tests gave equally erratic results among the abnormal subjects. The specific gravities of the Addis tests of the first group averages 1.020 and ranged 1.014 to 1.025, with a standard error of the mean of ±0.00063. Injection of surgical pituitrin was associated with concentrating ability that averaged 1.018 and ranged from 1.011 to 1.022. The standard error of the mean for this group was ±0.00081. Results of the second test, which combined 5 hours of fluid deprivation and injection of pitressin in oil, averaged 1.015 and ranged from 1.008 to 1.023, comparing favorably to the mean of the Addis test, 1.016 (range 1.008 to 1.025). However, this slight difference assumes significance in the presence of renal disease extensive enough to depress concentrating ability to this degree. Further, in 3 of 11 cases the Addis test gave readings 0.003 or more greater than the experimental procedure while none of the latter were superior.

Combination of 12 hours of fluid restriction and injection of pitressin in oil caused an average concentration of 1.018 with a range from 1.008 to 1.028. The standard error of the mean was ±0.00068. Results of the Addis tests of this same group averaged only slightly higher, 1.019. However, in 19 of 47 cases, the results of the Addis test were 0.003 or more greater than those of the experimental procedure, and the standard error of the mean was slightly less, ±0.00061.

Deprivation of fluid for 12 hours resulted in specific gravities that ranged from 1.006 to 1.033 and averaged 1.017, as compared to the mean value of the Addis test of 1.020 (range 1.015 to 1.025). The Addis test gave readings of 0.003 or greater in 16 of 30 subjects, and the standard error of the mean of the Addis tests was ±0.000607, as compared to ±0.0011.

In 4 of 47 patients, the combination of pitressin tannate in oil and 12 hours of fluid was associated with the formation of urine, the specific gravity of which was 0.003 or more greater than that collected following 24 hours of fluid deprivation, and in 4 of 30 cases 12 hours of fluid deprivation alone caused greater concentration. However, these 4 patients underwent the 3 tests on 3 successive days in the following order: Addis test, 12 hours fluid deprivation, and 12 hours fluid deprivation with subcutaneous injection of 0.5 cc. of pitressin tannate in oil. The procedures were thus separated by only 12 hours of normal fluid intake. The results may have been altered in the

direction of increasing urinary concentration by the succeeding periods of abstinence from fluid.

As indicated in Table 3, the outputs of urine resulting from antidiuresis induced in the same subjects by pituitrin and by water deprivation varied in an unpredictable manner. In 3 cases the injection of pituitrin reduced urine formation to the same degree as restriction of water. The specific gravities of these 3 specimens equalled or exceeded that of the Addis test. However, among the remaining 7 subjects, the results were inconstant. The urinary outputs during the pituitrin-induced antidiuresis varied between 40 and 300% greater than that during the Addis test, and the specific gravities of the samples were 0.004 to 0.014 lower.

TABLE 3.—URINE CONCENTRATIONS WITH THE ADDIS AND PITUITRIN TESTS

	Volume and specific gravity of urine formed during last 12 hrs. of Addis test		Volume and specific gravity of urine formed during a 12 hr. period of pituitrin antidiuresis	
	Volume (cc.)	Specific gravity	Volume (cc.)	Specific gravity
1	680	1.015	1425	1.0115
2	230	1.019	740	1.013
3	525	1.025	1610	1.011
4	275	1.028	420	1.024
5	180	1.024	470	1.0195
6	440	1.016	430	1.016
7	640	1.019	600	1.0204
8	320	1.026	460	1.027
9	230	1.026	440	1.022
10	180	1.029	190	1.027
Average	370	1.0217	678.5	1.0192

Pituitrin, in addition to its antidiuretic quality, is known to stimulate smooth muscle. This action was unpleasantly manifested in some of those patients who received as little as 10 units of surgical pituitrin. Seventeen of 41 persons complained of gastro-intestinal symptoms, ranging from abdominal cramps and frequent stools to incapacitating diarrhea. Five of the 41 subjects mentioned tightness in and about the precordium, but found no difficulty in carrying on normal activity. Other side effects of less consequence were pallor, giddiness and excessive perspiration. No reactions followed the use of pitressin tannate in oil.

Discussion. The accuracy of the Addis test of ability of kidneys to concentrate urine has been well documented by its author[1] (1926) and by Alving and Van Slyke[2] (1934), and has been used in this clinic for many years. Its value and reproducibility are attested by comparison of specific gravity measurements thus obtained with an independent tubular function, that of secretory capacity for diodrast. A quantitative interpretation of maximal urinary specific gravity has been provided by Corcoran and Page[5] (1942). They reasoned that concentrating ability should parallel tubular secretory capacity as measured by diodrast Tm and that it should be inversely proportional to a function of filtration rate as measured by inulin or urea clearance. They were able to demonstrate such a relationship, and developed a formula

whereby tubular secretory capacity could be predicted from specific gravity and urea clearance. Among patients with renal disease, and especially those with hypertension, the estimation of tubular function thus provided is of great significance. A substitute for an established concentration test should not be accepted unless it is equally reliable and neither more unpleasant nor hazardous to the patient than the older Addis procedure.

Shorter periods of fluid restriction, the injection of antidiuretic pituitary extract alone or in conjunction with short periods of abstinence from fluid, failed in our observation to promote the concentration of urine by normal persons to the same degree as did the Addis test (mean 1.025 compared to 1.030). If these tests had induced a consistent, albeit lower degree of urinary concentration, they might have been acceptable. However, among the normal subjects who received surgical pituitrin, the maximum specific gravity ranged from 1.015 to 1.033, as compared to a range of 1.026 to 1.032 following 24 hours of fluid deprivation. This discrepancy persisted in all tests in which pituitary extract or shorter periods of fluid deprivation were employed.

Injection of surgical pituitrin often produced such side reactions as skin blanching, abdominal cramps and diarrhea, at least as disagreeable as deprivation of fluid for 24 hours. A feeling of constriction about the chest occurred in 5 of 41 patients and called to mind the intense coronary vasoconstriction demonstrated in dogs following injection of pituitrin (Anrep and Stacey,[3] 1927, Gruber and Kountz,[8] 1930, Melville,[10] 1933, and Wegria, Essex, Herrick and Mann,[15] 1940). Temporary reduction of coronary blood flow through diseased vessels might precipitate thrombosis, myocardial injury, or serious cardiac irregularity. It is apparent that fluid deprivation does not endanger the hypertensive patient as may injection of surgical pituitrin.

Summary and Discussion. The ability of 33 normal and 65 abnormal persons to concentrate urine was measured by the Addis test, which necessitates water deprivation for 24 hours. These results were compared with those from the same patients in whom pituitrin, pitressin in oil, short periods of dehydration, and combinations of these were made in the hope that a less disagreeable test might be devised. None of these procedures attained the mean concentration of 1.030 recorded after 24 hours' dehydration in normal subjects. The range of variation in them was from 1.016 to 1.033, as compared to 1.026 and 1.032 in the Addis examination. Similar variability was observed in abnormal subjects receiving pituitary extracts.

It is concluded that substitutes for the Addis test which do not approximate the ceiling of specific gravity are not entirely acceptable in clinical practice.

We are grateful to Dr. W. A. Sodeman for helpful suggestions and comment.

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SOMATIC PAIN

Diagnostic and Therapeutic Aspects of Local Infiltration

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The use of regional block and local infiltrations to control somatic pain by means of anesthetic preparations has become widespread and the majority of reports is favorable. Application of this method yields excellent therapeutic results. The success or failure of regional infiltration depends on many factors, such as the nature and location of the lesion, the proper localization for infiltration, knowledge of pain pathways, the technique of injection, the interpretation of effects immediately following infiltration, factors which aggravate or prolong the pain, and the psychology and pain sensitivity of the patient.

Somatic pain, as a rule, is less difficult to interpret than visceral pain, so that usually an orderly approach can be made. One of the most valuable assets in determining the origin of somatic pain is knowledge of tenderness and its characteristics.

Tenderness. Tenderness is the main factor in determining whether an injection should be given locally, or whether a paravertebral nerve block should be used. Its pattern usually decides the location and origin of the painful stimuli. Its physical characteristics may indicate whether or not the pain is somatic or sympathetic. Tenderness completes the clinical picture so that attention is not focussed merely to the point of spontaneous pain.

An area may be said to be tender when sufficient stimulus is applied to elicit a painful response, the same stimulus failing to evoke a like response in a control zone, preferably one in a symmetrically identical area on the opposite side of the body.

Though skin tenderness may be mistaken for tenderness of underlying structures, the reverse rarely occurs. In neuralgic zones, especially of the segmental type, the location of the spontaneous pain may simulate pain of visceral origin.[2] This is especially true of the abdominal

wall neuralgias. As segmental neuralgia occurs frequently, it is of value here to discuss skin tenderness.

There are 2 types of skin tenderness: superficial and deep. In the superficial type there is tenderness to pinch when a fold of skin and fat is compressed between the fingers. There is also hyperalgesia of the skin demonstrable by pin-prick or pin-stroke. When pinching the skin in the superficially tender type a definite thickness of fat is usually present (Fig. 1). This type may also be tender to poking.

FIG. 1.—Eliciting skin and fat tenderness within a zone of segmental neuralgia. A liberal fold of skin and fat is compressed between the thumb and forefinger. Compare space between thumb and forefinger with that of Figure 2. It is in this type of skin, with the thick fat layer, that we usually find compression tenderness, poke tenderness, and tenderness to pin-stroke. (Judovich and Bates, Segmental Neuralgia in Painful Syndromes; courtesy of F. A. Davis Company.)

The second type, deep skin tenderness, is elicited only by poking or pressing the skin firmly against a muscle or bony structure and not by pinching nor by pin-stroke. When the skin is picked up between the fingers and pinched, there is little or no subcutaneous fat in the skin fold (Fig. 2). This type may be defined as pressure tenderness.

The tenderness in both the superficial and deep types follows an identical pattern as to area of distribution. To show that deep skin tenderness is in no way due to underlying muscle sensitivity, certain nerves were selected in areas where the skin and the underlying muscles each received a totally different nerve supply. For example, the distribution of D_{12} and L_1 nerves overlap the gluteus maximus muscle, which is supplied by L_4, L_5, S_1, and S_2. Paravertebral infiltration of D_{12} and L_1 nerves with 5 cc. of 1 or 2% procaine causes complete disappearance of deep tenderness in the segmental distribution.

Approximately 15% of patients show this deep skin tenderness. The tenderness may be in the deeper layers or in the superficial fascia,

or perhaps poking stimulates a different type of reaction. In this group, beeause the patient presents no superficial signs of tenderness, the diagnosis of a neuralgia may be overlooked.

Clinically we have found that interpretation of the origin of somatic pain is facilitated by dividing pain into 3 major groups: local, transmitted and reflex. From the viewpoint of this particular discussion they may be defined as follows:

Local Pain. The pain, or pain and tenderness remains confined to the area of involvement. Examples of this type are fibrositis, myositis and tendonitis.

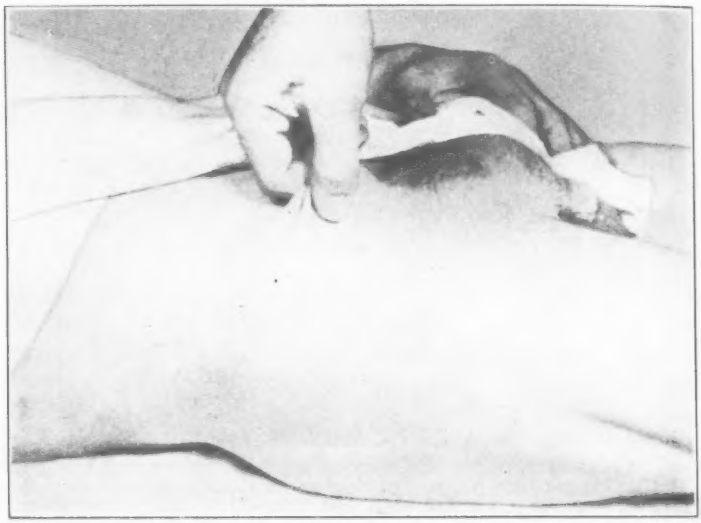

FIG. 2.—Testing the abdominal wall for skin and fat tenderness. Note the close proximity of the thumb and forefinger, which means that little or no fat layer is being compressed. It is in this type of skin that superficial tenderness is absent and deep pressure tenderness present, so that unless tenderness is properly elicited the zone of segmental irritation will be overlooked. (Judovich and Bates, Segmental Neuralgia in Painful Syndromes; courtesy of F. A. Davis Company.)

Transmitted Pain. The pain is carried along the course of a nerve, with either a segmental or peripheral skin pattern. This implies root or trunk irritation, or irritation in the course of the nerve either by intrinsic nerve changes or irritation by contiguous structures along its course. The pattern of distribution is determined by eliciting tenderness. Examples of this type of pain are the various types of chest and abdominal wall neuralgias, sciatic pain due to root or trunk irritation, occipital neuralgia, and brachial plexus neuralgia. Anesthesia, hypalgesia, hyperalgesia, trophic changes, motor involvement, and diminution or absence of reflexes may or may not be present.

Reflex Pain. Reflex pain is pain which is referred from an irritated somatic structure to a distant area within the same segmental innervation. An example of this type is pain which is referred from the hip joint ligaments to the lower leg. The area of referred pain is not asso-

ciated with tenderness. Reflex pain may also be referred from muscles, tendons and other local structures to distant areas of the same segmental innervation or contiguous levels with absence of tenderness in the zone of reference. Sensory, motor, and trophic changes do not involve the area of reference. Reflexes are not affected.

In occasional cases, the area of referred reflex pain may be associated with a markedly sensitive zone which has no neurologic topography and which cannot be classed under the heading of transmitted pain. These areas are probably due to the irritable focus of the lesion sending a bombardment of impulses to the spinal cord, affecting the sympathetic components of that particular segmental level, or contiguous levels, and the resultant irritation is expressed in the periphery by tenderness and pain which is probably vascular in origin.

Transmitted Pain. The factor which most often causes confusion in the interpretation and treatment of somatic pain is failure to establish its origin, so that a local infiltration does not produce the desired effect. Errors of this type do not occur often with local pain, but are usually made in the *transmitted type* of pain, often associated with segmental tenderness. In this type, although the source of pain is usually the nerve roots or trunks, the spontaneous pain may develop at any point within the segmental distribution, either in the anterior or posterior divisions. This, of course, is dependent upon which fibers are sufficiently stimulated to reach the pain threshold.

Case Reports. The 2 following case reports are used as illustrations of transmitted pain:

Case 1. S. L., physician, age 48. Chief complaint: Severe low back pain with radiation to anterior thigh. Duration, 7 weeks. Pain and tenderness of the anterior thigh to a point 4 inches above the knee joint. Previous treatment consisted of analgesics, physical therapy, and a sacro-iliac belt. His pain was diagnosed as sacro-iliac in origin. He was unable to wear the belt because of increased discomfort. The points of spontaneous pain involved the upper half of the buttock as far as the sacro-iliac joint medially and the anterior thigh. These areas were within a zone of tenderness which involved the 12th dorsal, 1st and 2nd lumbar dermatomes. There was trunk tenderness paravertebrally at points corresponding to the peripheral distribution. Paravertebral infiltration at these levels caused immediate cessation of pain. There was no recurrence after the first injection 4 years ago. Etiology undetermined.

If this condition had been a sacro-iliac sprain, the radiation which was associated with it should have been lower down, along the branches of the sciatic nerve. These branches, however, were unaffected in this particular case. As a further check, it was found that in the paravertebral level of L_1 and L_2 pressure inward toward the transverse processes caused severe pain. Diagrammatic details are given in Figure 3.

Case 2. E. C., female, age 45. Complaint: Pain in the left chest, precordium and back. Duration 3 years, with a history of a fall some time previous to the onset of symptoms. Exertion aggravated the pain. Occasionally she developed pain on the left side of the interscapular region. She took "needles" for heart trouble.

Examination revealed segmental tenderness from D_3 to D_8. There was contralateral tenderness of the dorsolumbar region involving D_{12} and L_1 on the right side due to an S scoliosis. There was a $\frac{1}{2}$ inch shortening of the left leg. A heel raise, with no other form of therapy caused complete cessation of

pain in less than a week. Had this patient not made a recovery with correction of her postural defect, the site of infiltration would have been in the paravertebral area, selecting those nerve trunks supplying the painful segments. (See Figs. 4 and 5.)

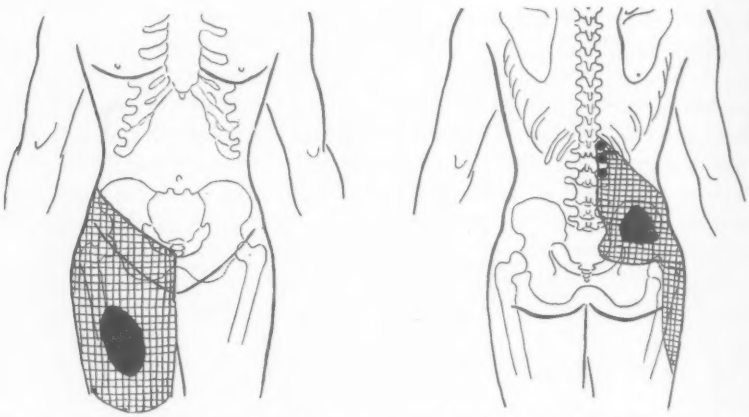

FIG. 3.—(Judovich and Bates, Segmental Neuralgia in Painful Syndromes; courtesy of F. A. Davis Company.)

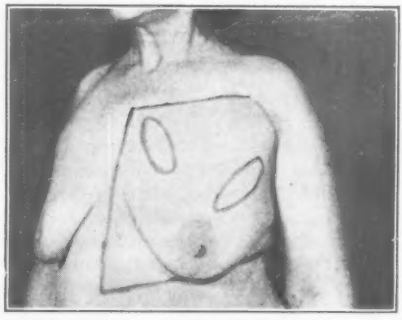

FIG. 4.—Outlined area is the zone of segmental tenderness. The oval areas represent the points of spontaneous pain.

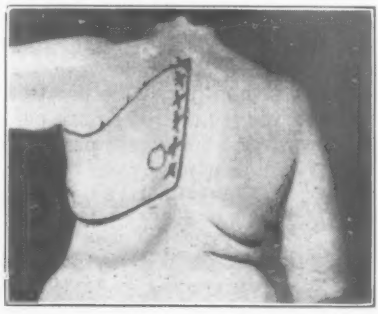

FIG. 5.—Outline shows segmental tenderness posteriorly. Oval area represents area of occasional spontaneous pain. Crosses indicate posterior division tenderness in paravertebral area.

Reflex Pain. The following case serves as an excellent illustration of reflex pain.

CASE 3. M. D., male, age 32. Chief complaint: Severe pain in the right shoulder and arm radiating to the thumb and forefinger. Duration 6 months, with gradual increase in the severity of symptoms. On his initial visit, he stated that his pain was intolerable; it first started over the deltoid muscle, later spread over the clavicle, scapula, neck and to the biceps above the elbow. Two months later it radiated to the thumb and forefinger. Motion of the right shoulder joint had not become limited until his 5th month of pain. There was some difficulty in adducting the arm to the side of the body, especially against counterpressure. There was no history of injury or other factors which precipitated the onset. He had previously had Roentgen ray studies which were found to be negative. In spite of many forms of therapy, he obtained no relief.

When first examined, he had severe pain of the entire shoulder, arm, forearm, thumb and forefinger. However, none of the painful areas were associated with tenderness, except for a small area the size of a half dollar, above and below the middle of the spine of the right scapula. There was no tenderness along the cervical spine, or the paravertebral area. The scalenus anticus syndrome was absent. The reflexes were normal. Routine blood studies were normal.

Infiltration with procaine of the tender region around the spine of the scapula gave partial relief which lasted only for ½ hour. Further Roentgen ray studies of the cervical spine in the antero-posterior, lateral and oblique projections showed no abnormalities. There was a small localized area of demineralization in the spinous process of the scapula. After another Roentgen ray and comparison with the scapula on the opposite side, the diagnosis was made of destructive lesion of the scapula, probably a sarcoma.

At operation the region in the spine of the scapula was found to be necrotic and a large mass was found involving the subscapularis muscle. The entire scapula was removed except for the glenoid fossa. This was followed by Roentgen ray therapy. The microscopic diagnosis was osteogenic sarcoma.

The patient was in excellent condition 14 months later. There has been no loss of weight, and no evidence of recurrence.

This is an example of pain being reflexly referred from one somatic structure to distant areas of the same segmental innervation without the presence of tenderness.

Combined Somatic and Sympathetic Pain. Another group of cases which may present a confusing clinical picture, is that showing mixed types of pain, somatic and sympathetic. This is usually found in the extremities, especially the upper. Pain of vascular origin may be combined with pain of nerve origin so that the resulting syndrome is difficult to evaluate upon an anatomic basis. This is often caused by a spastic anterior scalene muscle which is secondarily affected by local shoulder joint lesions such as tendonitis, myositis, fibrositis and bursitis. Superficially, the symptoms might be those of a brachial plexus neuralgia, or of a bursitis or tendinitis associated with it. Yet, neither a brachial plexus block, nor an injection of the bursa or tendon will control the pain, nor will it give the desired diagnostic information. Infiltrating the anterior scalene muscle with procaine, however, will cause relief of pain in the scapular, infraclavicular lower arm and hand. If any other local lesion about the shoulder joint is present, it will not be relieved and it can be more sharply localized, the overlap of

vascular and neuralgic pain and tenderness of the scalenus syndrome having been erased for the time being. Example of mixed types of pain are illustrated in the 2 following cases:

CASE 4. A male, 45 years old, glass blower, complained of severe pain in the left arm and shoulder of 2 years duration. The pain started around the elbow and upper forearm, and was associated with a numb feeling and coldness of the first 2 fingers. The grip was not impaired. For 2 months he has had some stiffness of the neck with pain in the upper scapular and supraclavicular region. The pain had become very intense and he walked the floor every night for several weeks. Lying down would cause terrific pain in the shoulder blade and upper chest. As it became more intense, the pain spread toward the spine around the level of the first and second dorsal vertebræ. Some days the arm felt like a dead weight, "as though it were going to drop off."

Previous treatment consisted of baking and injections of thiamine, with no relief.

Examination. Retracting the head to the right caused shoulder and arm pain. Compression of the scalene insertion on the left was very tender as compared to the right. Pressure caused severe intensification of his pain. The upper chest below the clavicle, and the dorsal surface of the upper forearm were tender. There was no tenderness below this point.

Dynamometric reading of the left hand was 100; the right, 140. In spite of the fact that his first two fingers felt cold, numb and tingled, there was no difference of temperature with thermo-couple measurements as compared to the right hand. There were no alterations of skin sensation. The biceps and triceps tendon reflexes responded normally.

Roentgen ray of the cervical and upper dorsal spine was essentially negative. Wassermann test, blood count, blood sugar and blood sedimentation rate were normal.

This case presented typical symptoms of a scalenus anticus syndrome. However, when the scalene muscle was infiltrated with 1.5 cc. of 2% procaine, the neck, shoulder and upper arm pain disappeared in about a minute, but the pain around the elbow and the upper arm, and the "coldness" and numbness of the first 2 fingers persisted. Examination of the elbow revealed a very tender epicondylitis. Rolling the extensor muscle attachments under the thumb in this area, caused tingling of the first 2 fingers. Injection of 3 cc. of 2% procaine into the extensor attachments caused almost immediate disappearance of the pain in the elbow region. The cold sensation and tingling in the first 2 fingers disappeared as soon as the anesthetic took effect. The painful symptoms and paresthesias did not recur. The sensation in the fingers was undoubtedly due to *reflex paresthesia.*

Thus, a group of symptoms which presented all the characteristics of a brachial plexus neuralgia or of a scalenus anticus syndrome, proved to be neither. An accurate diagnosis would have been impossible had not the overlapping scalenus syndrome been first erased from the picture.

CASE 5. Another example of mixed pain was a patient with controlled diabetes, who complained bitterly of pain in the entire lower extremity. The pain was associated with a burning sensation often described by patients suffering with this disease. Examination revealed a positive Lasègue sign, no atrophy, normal Achilles jerk. The skin of the entire extremity was hypersensitive.

Following his first sciatic infiltration, he obtained marked relief of pain. The pain in the anterior thigh and leg persisted. Infiltration of L_2, L_3, and L_4 nerve trunks for this distribution gave further relief of the neuralgic pain in this area. Throughout all of his treatment he still complained of the intense

burning sensation on the anterior leg from the knee to the instep. Associated with this was another area on the internal surface of the knee. Neither of these areas had any particular distribution that would suggest either peripheral or segmental nerve involvement. Either by mild or by firm pinching, sharp pain was elicited. However, firm compression of the skin against the bone, with extreme force, caused no pain. In spite of the fact that all trunks from L_2 down had been injected, and his neuralgic pain was definitely relieved, the annoying burning sensation had never subsided. We felt that this pain might be sympathetic in origin.

Following this, L_1 and L_2 sympathetic ganglia were infiltrated, using 5 cc. of 2% procaine at each area. Within a few minutes the burning sensation completely disappeared, with no recurrence reported for several months.

Combined Reflex and Transmitted Pain.

Case 6. In 1 patient, who complained of severe pain in the back, hip, and leg, we were able to demonstrate both pain and segmental tenderness due to a spinal lesion, and pain without tenderness referred from the hip joint of the same side. The patient stated that the pain traversed the entire leg anteriorly to the front of the ankle, along the course of the anterior crural nerve. Yet upon elicitation of tenderness, a segmental area involving the 3rd lumbar distribution was all that could be found. Here was segmental tenderness associated with the pain of a peripheral distribution without tenderness. The lowermost portion of L_3 distribution ends some distance above the lowermost distribution of the anterior crural nerve and would not account for the pain in the lower anterior leg.

Examination revealed that the spinous processes of L_3 and L_4 vertebræ were very tender to pressure. A positive Patrick's sign was obtained on rotation and abduction of the hip joint. The knee-jerk was absent on the painful side.

Roentgen ray of the spine revealed a marked narrowing of the interspace between L_3 and L_4 vertebræ with bridging of bone. The rest of the lumbar spine was normal. The hip joint showed almost complete destruction of the cartilage, so that the head of the femur rested upon the acetabulum. Thus, we had a spinal lesion with reference of pain to the lower extremity with a definite segmental zone of tenderness and a hip joint lesion with reflex reference along a peripheral nerve which was not associated with tenderness.

Infiltration of the ligaments of the hip joint caused immediate cessation of the pain in the lower third of the leg. The pain just below the knee, however, persisted. Following the infiltration of the 3rd lumbar nerve trunk paravertebrally, this pain was also erased.

Low Back Pain. Low back pains may be classified into 2 types: those wi h radiation, and those without. The radiating pains may be of reflex or transmitted type. Areas which may be affected by radiating pains are the iliac crest, the lower quadrant of the abdomen, and the anterior or posterior aspects of the lower extremity.

The areas of referred pain may or may not be tender. If tenderness is present in a segmental pattern (transmitted pain), it signifies that there is irritation of the roots or trunks and that therapy should be directed to the spinal area. In these cases paravertebral tenderness is found at levels which correspond to the peripheral distribution. Hence, local infiltration or any other therapy applied to peripheral areas of spontaneous pain prove to be of little therapeutic value.

In low back pain without radiation, areas of local tenderness usually can be elicited. Areas frequently involved are the spinous processes, the lumbosacral or sacro-iliac junctions. Soft tissue syndromes such

as myositis and fibrositis are often observed. Tenderness in these areas is usually limited to the particular structure which is irritated. If injection therapy is to be employed, local infiltration should be used. Nerve block will be of little value (Figs. 6 and 7).

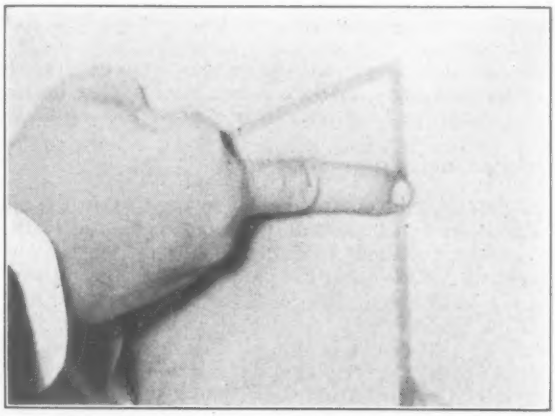

FIG. 6.—Pressure or fist percussion over spinous processes causes a painful reaction when applied at levels within a zone of segmental tenderness.

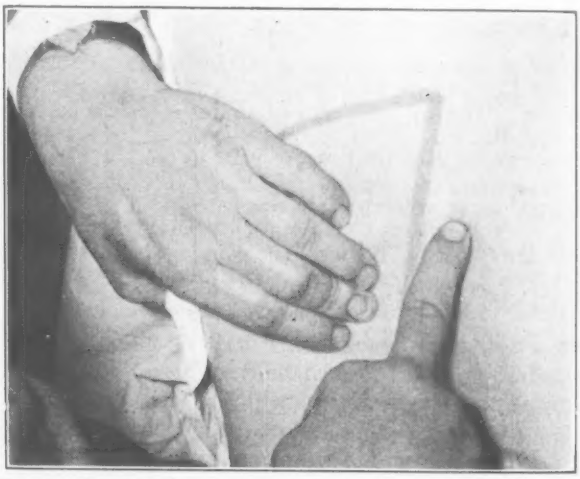

FIG. 7.—Keeping the palpating finger at the same point and pulling the normal skin over to the painful side causes the pain on pressure to disappear, which demonstrates that the tenderness is in the skin and not in the structures beneath.

A local infiltration of procaine into these areas is not always conclusive of the fact that these areas are the cause of the pain. Procaine does curious things. In patients with segmental neuralgia, where we are certain that the irritating focus is either in the spine or in the paravertebral area, a local infiltration of procaine into the peripheral area of pain, even at points in the anterior division, may cause cessa-

tion of pain in the entire segment. However, the patient does not obtain prolonged relief of pain and often has a flare-up following the subsidence of anesthesia. A paravertebral infiltration in the same patient, selecting the involved nerve trunks, yields a much more satisfactory result.

This observation is in accord with those of Livingston,[6] who, in a recent monograph on "Pain Mechanisms," states that he has injected procaine distal to a nerve lesion and secured temporary alleviation of symptoms. He also quotes Mitchell[7] and Tinel's[8] relief of pain by cutting a nerve distal to a known lesion of the nerve trunk causing the pain.

Lewis[4,5] states that, although the hyperalgesia due to local injury may vary in extent according to the degree of injury, it remains within the distribution of a single peripheral nerve, or one of its branches, and never extends into the territory of adjacent nerves. From Lewis' statement, it would appear that a local lesion in the periphery, although it could cause areas of pain reference, would not set up tenderness of a segmental distribution.

In low back pain having its origin at the dorsolumbar area, the patient's complaints may so closely simulate those of sacro-iliac pain that diagnosis may be difficult. If the dorsolumbar irritation affects the lower abdominal quadrants, the pain may simulate pain of any of the underlying viscera.

Many of us are familiar with the story of the laborer, who after heavy lifting suddenly develops acute pain in the groin. He is immediately examined with the expectation of finding a hernia. The examination reveals nothing—just pain; but if we look for it, segmental tenderness will often be found in the distributions of D_{12} and L_1. This is as much a back sprain as any condition in which backache is the complaint, except for the fact that the anterior fibers are the ones which develop spontaneous pain.

The fact that many back sprains are associated with segmental pain and tenderness gives us reason to feel that the location of the tissue injury in these cases is deep in the paravertebral area, close to the nerve trunks as they emerge, or intraspinal, as in the case of a ruptured disk. Local injury to muscles, tendons, or ligaments, if it does not irritate the nerve trunks, may cause segmental pain but does not appear to cause segmental tenderness.

Patients who permitted injections of irritant materials into various areas only occasionally developed pain reference of nerve reflex mechanism. For example, 10 patients were injected with 0.5 cc. of 6% sodium chloride intramuscularly (a method reported by Kellgren). In only 1 case did there appear to be pain of nerve reference. This particular patient was injected paraspinally at the level of the first lumbar vertebra and the injection caused pain to spread through the posterior division of this segment. The pain, however, was not associated with the least bit of tenderness.

The rest of the patients received injections intramuscularly at the site of the gluteal muscle or at different levels in the paravertebral

region. As we have stated, only 1 patient in 10 had referred pain, and this was confined to the posterior division of the segment injected. The other patients had some local pain for 1 to 2 minutes, which spread for only a short distance from the site of injection, not more than 4 or 5 inches, and appeared to be confined to the limits of the muscle. In no case was pain referred to the anterior division. In 4 patients, the area of the interspinous ligaments were injected with the saline solution. In 2 cases pain reference was to the abdominal wall, but in neither case was there segmental skin tenderness associated with the referred pain. In another patient the fascial plane was injected at the level of L_1 paraspinally, according to the technique of Kellgren.[3] Pain reference was obtained in the posterior division of the first lumbar nerve only, and it was not associated with skin tenderness, either deep or superficial.

We have observed anterior nerve reference of pain in patients who received gluteal injections of liver and bismuth. The patients stated that the pain traveled down the leg to the calf. Examination at the time revealed that the area of pain reference was not associated with tenderness.

Differentiating the source of pain according to the presence or absence of tenderness has been a more satisfactory working basis than mere attention to the area of pain. This conclusion is supported by observing and treating patients with old back injuries long after the acute disturbance has subsided. Segmental pain and tenderness may persist for months or years in these cases. Any efforts directed to areas of spontaneous pain in the periphery of the segment are of no avail in clearing up the pain. It is true that local infiltrations will cause temporary cessation of pain, but this is no source of satisfaction to the patient, since it is of short duration and is often followed by an aggravation of pain.

On the other hand, attention being directed to the paravertebral area, infiltration of the nerve trunks responsible for the segmental tenderness causes prolonged relief, often curing the complaint of pain. Chances of permanent relief are further enhanced when existing postural defects are corrected. Commonly a heel lift for a shortened extremity is of great aid. The short leg produces a mild scoliosis, often ignored, but, nevertheless, sufficient to be the cause of the pain. Many of our patients have had pain recur after forgetting to have the heel lifted in new shoes.

This phenomenon is often the explanation of why patients with segmental pain and tenderness of the lower right abdominal quadrant, with pain of months or years duration, are told by their physicians that they are suffering with chronic appendicitis. The patient may wander to an osteopath who, by treating the spine—perhaps baking, massage, and a heel lift—may cause the pain to subside or disappear. We frequently hear such patients state that their "appendicitis" was cured by an osteopath. The original erroneous diagnosis of appendicitis, was of course, to blame.

In segmental pain and tenderness, nerve block has provided more

rapid relief of pain and rehabilitation of the patient than any other single method we have employed. One mechanism by which the pain is relieved in acute sprains was suggested by Leriche, when he advocated local infiltration of procaine for the treatment of sprained ankles. He stated that the swelling and the period of disability were diminished or completely controlled by this method. His concept of local injury is that a vicious cycle is established at the site of injury, incorporating the usual excitor, connector, and effector stimuli; the effector stimulus being transmitted throughout the sympathetic system. Thus, when a sprain takes place, the stimuli from the point of injury send afferent impulses back along the segment to which they belong. This in turn causes stimulation of the sympathetic efferent fibers, which returns impulses to the vascular system at the point of injury, producing swelling and increased pain.

Whatever the mechanism, it is a fact that the local anesthesia does produce rapid symptomatic relief and shortening of the period of disability, often allowing patients to continue with activity rather than putting the part to rest. Infiltration applied to back sprains acts in the same manner.[1] Often, if the patient is seen and treated soon after the injury, severe pain can be controlled and prolonged disability prevented.

Failure to Obtain Relief. Failures should be investigated from several angles. If a paravertebral nerve block does not give relief of pain within 5 minutes and the segmental tenderness still remains, the nerve has not been properly infiltrated.

If the segmental tenderness disappears and the pain still persists, it may be caused by: (1) A lesion proximal to the point of infiltration, which would be intraspinal. (2) A local lesion which is overlapped by a zone of segmental neuralgia. In this event, examination for a local lesion or point of tenderness should be made during the period in which the segmental tenderness has been anesthetized. (3) A visceral lesion which may coëxist with the segmental neuralgia. (4) Medicolegal complications, where the patient refuses to admit relief of pain. Malingering will not produce segmental tenderness, but the patient may exaggerate the degree of pain. Hysteria does not produce segmental neuralgia and is usually accompanied by other diagnostic signs. (5) If the patient obtains relief of pain and disappearance of segmental tenderness, and the pain recurs shortly after the anesthesia subsides, an intraspinal lesion must be kept in mind. Many cases of ruptured intervertebral disks have had such a reaction following nerve block. Metastatic lesions of the spine may exist for months without Roentgen ray evidence. The duration of relief is also influenced by the nature of the fluid injected. If the pain is due to a postural defect, injection alone does not usually cause complete control of the pain. Correction of postural defects increases the incidence of permanent relief. Many patients develop pain following an upper respiratory infection, the onset of pain usually developing 1 or 2 weeks later. Unless questioned specifically, this information may not be volunteered by the patient.

Somatic pain may arise from any disease process, toxic absorption or mechanical disturbance which directly or indirectly causes irritation of any of the skeletal structures. In spite of careful search, the causative factors in many cases cannot be discovered.

Summary and Conclusions. 1. Tenderness has been stressed as the basis of classifying somatic pain into local, transmitted and reflex types. In the author's experience, this concept has facilitated diagnosis as well as therapy. Case reports have been cited to illustrate its clinical application in each type.

2. Local infiltration and paravertebral nerve block are efficient methods of controlling certain forms of somatic pain. The method is often of value in differential diagnosis. Failure to obtain relief of pain following nerve block may also be of diagnostic value.

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PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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REFRIGERATION IN SURGERY

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The increased use of reduced temperature in surgery has renewed interest in the effects of temperatures other than those which are considered normal for mammalian tissues. The use of hot or cold applications in surgery is ancient in origin. Despite this fact, the effects of such applications have not been thoroughly understood. The efficacy of heat or cold as therapeutic agents, while recognized, was not well-enough defined to prevent controversy over the temperature which was most useful in any given case. Temperatures low enough to cause freezing or high enough to cause burns were always recognized as pathologic. Therapeutic interest is concerned with the range of temperatures between these extremes. Attempts to affect the course of disease by changing the temperature of the entire body have yielded useful information regarding reactions to heat and cold regardless of the advantages which may have resulted so far as therapy is concerned. Supplementing the excellent observations made by Bazett,[4] careful physiologic observations have been made upon patients undergoing hyperthermia induced for therapeutic reasons.[6,22,23,49] More recently an opportunity for similar studies has been afforded by the introduction of treatment by hypothermia by Fay and Smith[18,46] in 1938. Recent studies of the effects of cold have been made by various authors.[5,7,15,16,20,21,27,28,31,36,41,42,43,45,48]

Cold applications have been frequently used to allay pain in clinical medicine. In fact, the use of cold applications to the right lower quadrant has long been considered a dangerous procedure in cases of acute appendicitis because it decreases the pain and, therefore, may mask the symptoms of a progressing inflammatory process in the appendix. Penetration of the reduced temperature to the inflamed area is not likely[10] and might not be expected to influence the inflammation. The numbing effects of cold have been commonly experienced with the extremities, the nose and the ears being most subject to insensibility from exposure to cold.

Cold applications have been used in superficial inflammatory lesions, frequently without too clear a concept of their effects. There are strong advocates for the application of heat in the treatment of superficial infec-

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tions, and possibly fewer but just as strong advocates for the use of cold. Such controversy is not new. Hot applications up to 40° C. tend to produce a sense of warmth, an increase in cellular activity, and a greater flow of blood to the area; cold, on the other hand, has a tendency to cause opposite effects. Vasoconstriction is found with moderate cold as evidenced by blanching; but vasodilation is also found, especially in colder temperatures.[31] The use of moderately cold applications is useful early to prevent exudation and swelling in non-bacterial inflammation; in infection, cold is likely to do more damage than good because, while it tends to depress the activity of bacteria, it likewise depresses the activity of the tissues and, though it has long been known to inhibit bacterial growth, even freezing temperatures do not kill the common pathogenic organisms. Cold likewise inhibits cellular activity, but freezing causes death of cells. Therefore, if death of the organisms is the aim, little success can be anticipated from cooling infected tissues in the light of the differential response of organisms and tissues to cold. In addition, decreased resistance to infection has been reported to result from cooling.[37]

Studies reported by Large, Bruneau, and Heinbecker indicate that there is delay in the healing of wounds[30] and a greater susceptibility to infection after refrigeration.[13] They found that immersion of dogs' legs in water maintained at 6° C. for 96 hours resulted in edema, depression of motor and sensory function, and degeneration of nerves in the cooled areas. They believe these changes to be due to ischemia. Tissues cooled to 6° C. did not show the usual inflammatory response seen after inoculation of *Strep. hemolyticus*. The number of organisms present remained the same. After the tissues were permitted to warm, there was a decrease in the growth-restricting power of the tissues to the organisms and a more marked inflammatory reaction than usual. Brooks and Duncan[12] also report findings which indicate that in refrigerated tissues there is a more severe inflammation after warming to environmental temperature than was present in areas not subjected to cooling. Many of the experiments of Heinbecker and associates[13,30] were carried out with the limbs immersed in cold water, and thus approximated the conditions responsible for immersion foot in the cases studied by Webster and his associates,[50] and by White.[52] While the tissues might be cooled more effectively in a water bath than when surrounded by ice, and are in a more dependent position than is common in clinical practice, the situations appear otherwise comparable.

The use of artificially induced low temperatures in the treatment of arteriosclerotic gangrene of the lower extremity has been a definite surgical advance. Cooling of a large part of the extremity to temperatures just above freezing is a procedure which was not thought advantageous or possible before the work of Fay and his coworkers[18,46] proved that the human could stand marked lowering of the general body temperature, and indicated that lowered body temperature could be maintained for long periods without obvious damage to normal tissues. These studies, though conceived with the erroneous idea that the course of patients suffering from cancer could be altered beneficially, are important because they renewed interest in the general problem of hypothermia. Allen,[2] in 1939, and Brooks and Duncan,[11] in 1940, demonstrated that necrosis of animal extremities resulting from ischemia occurred after a much longer period of time in the cooled extremity than in the extremity maintained at room temperature. He pointed out that the blood did not clot in the cooled extremity, and that such an extremity was insensitive to pain, so

that amputation without other anesthesia was possible. This knowledge was applied to the problem of the bad risk patient requiring amputation. Allen and his coworkers[3,14] performed amputations under reduced temperature with a tourniquet applied on 45 poor-risk patients with only 7 deaths (15.5%). The authors were impressed with the ease with which the amputations were carried out and the absence of shock in the patients. Numerous reports of the use of the method, especially in arteriosclerotic gangrene, have been enthusiastically presented.[24,25,26,32,35,39,40,44,53] McElvenny[34] reported a case of amputation of both legs for trauma where cooling without a tourniquet was a factor in controlling shock and permitted delay in cleaning up the stumps. While the most obvious application of refrigeration in surgery is that associated with amputation, the method has been applied in other conditions of importance. Probably the most timely is the treatment of immersion foot by cooling of the affected part, which has become the accepted form of therapy.[50,52] Recently Webster[51] has utilized refrigeration for preservation of skin grafts.

It is unfortunate that the term "refrigeration anesthesia" has been applied to the procedure recommended by Allen, for actually the anesthesia afforded is not the most important factor. The tourniquet tightly applied is of great importance in cases where there is likely to be absorption from a gangrenous or badly infected leg. The importance of the tourniquet in this regard is stressed by Maxeiner[33] and by Adolph[1] who reported its use in a case wounded in the Sino-Japanese war.

Important facts which have received too little attention in the past have been more widely appreciated through the interest which Allen's work has stimulated. For years it was an all too general custom to warm legs, the blood supply of which was limited in one way or another. The fact that metabolic needs increased with increase in temperature was well understood, but this fact was not generally considered in treatment of cases of arteriosclerotic gangrene. It is interesting that Starr[47] made the following sage comment in an article describing a thermoregulated heat cradle for use in such limbs: "The considerations which should govern the therapeutic application of heat in peripheral vascular disease are not identical with those which obtain in conditions in which the blood supply is normal. If the vessels are inadequate to carry sufficient blood to meet the increased oxygen demands of heated tissues, positive damage may result from degrees of heat which would be beneficial, were the blood supply more nearly normal. It is well known that 'baking' a foot with undiagnosed peripheral vascular disease may cause gangrene; I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized."

Freeman[19] reëmphasized this concept with relation to treatment of peripheral vascular disease. During the last war and following it, great emphasis was placed on the application of heat to patients in shock. For years this concept was taught as important in the treatment of shock. Early in the present war, definite evidence of the harmful effects of increased heat in the treatment of shock was presented by Blalock.[8,9] Elman and associates[17] presented data indicating the harmful effects of heat used in the treatment of burns. Lesions in which there is interference to the blood supply are also found to respond poorly to increased temperatures as was so aptly shown by the work of Brooks and Duncan.[11]

While it has been shown that a limb without blood supply will survive longer if cooled, damage does result in time. Even if the part is adequately cooled, the application of a tourniquet presents dangers to survival of

tissue below it if left on for long periods of time. Whether or not the part should be amputated should determine the length of time the tourniquet is allowed to remain.

Brooks and Duncan[11] have reported microscopic changes in ischemic rats' tails even though refrigerated, and warn against too broad clinical use of the tourniquet with refrigeration. They suggest that it is possible that tissue necrosis may result but not be apparent. Richards,[44] in a study of 1 case, believed that he had found evidence of fibrosis of nerve and muscle tissue after ischemia produced by a tourniquet and refrigeration. Large and Heinbecker[29] are of the opinion that the advantages of refrigeration with a tourniquet applied are sufficiently great to eliminate concern over whether or not there is production of anesthesia by means of cold for the amputation. They feel that amputation should be done above the level of the constricting tourniquet and under the usual methods of anesthesia. They do not advocate prolonged cooling of tissues to be preserved because of the delay in wound healing and the lowering of tissue resistance to bacterial invasion. This seems a conservative viewpoint on a sound basis, especially since one of the important advantages of the use of refrigeration and tightly applied tourniquet is that it converts the patient to a better surgical risk.

It is interesting to note the concept concerning the use of cold as presented by Dr. Nancrede to the students at the University of Michigan previous to 1899 in his "Lectures Upon the Principles of Surgery:"[38] "Cold, however, is a most potent remedy when judiciously employed, yet it must not be so intense as to act on the vessels directly through the medium of the overlying tissues, but by impressing the cutaneous nerves and reflexly causing contraction of the vessels. For instance, no amount of cold which could be endured would directly influence the intracranial circulation, hence a moderate degree of cold is all that is requisite. Cold so applied as directly to abstract enough caloric to influence deep seated vessels or those at the center of a more superficial inflammation would lower the cell vitality of the part, favor the cohesion of leucocytes, and diminish ameboid activity. It should therefore, always be employed with caution in parts whose vascularity is normally poor and where decided strangulation of tissue has resulted from extensive and rapid exudation lest stasis be precipitated and gangrene result. When employed in proper cases, cold relieves pain by reducing the hyperemia of the nerves and thus their increased registering power."

Our knowledge of the principles regarding the effects of cold have changed little. Many new facts have been presented with regard to the effects of controlled low temperature, and the reaction of tissues to these temperatures. Clearer concepts regarding the benefit which may be expected from refrigeration are at hand. There is, however, much to be done relating to the determination of the limits of safety and extension of usefulness of refrigeration in surgery.

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OPHTHALMOLOGY

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RETINOPATHY IN GLOMERULONEPHRITIS

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Considerable confusion still exists concerning the nature, occurrence and mode of development of retinal lesions in cases of glomerulonephritis, especially of the chronic type. This confusion has been due in part, undoubtedly to the persistence among many ophthalmologists of the idea that "albuminuric retinitis" is always evidence of disease of the kidneys and that it never occurs in the absence of renal insufficiency. In other words, the presence of "albuminuric retinitis" is considered in itself to be diagnostic of "chronic nephritis." This idea, however, is becoming less prevalent and the predominant rôle of vascular hypertension in the pro-

duction of the retinopathy is being more generally recognized. This very fact has tended again to confuse the issue as to the incidence and nature of retinal lesions in glomerulonephritis, since many observers think that the lesions are identical with those occurring in primary hypertensive disease and make no attempt to differentiate them. Thus there are two schools of thought, one asserting that all the vascular retinopathies are "renal" and the other that they are "hypertensive" in origin, that is, caused by the elevation of blood pressure in itself.

Two other factors share part of the responsibility for the confusion. Variations in the interpretation of the ophthalmoscopically visible changes and in the terminology used to designate them make it difficult to compare the findings reported by different authors. And last, the difficulties inherent in the clinical diagnosis of chronic glomerulonephritis and its definite differentiation from the terminal stages of primary vascular disease result in considerable uncertainty as to the incidence of the various types of retinal lesions in cases of pure glomerulonephritis. As Ellis states, "A major difficulty in the understanding of Bright's disease is that different renal disorders may, in their late stages, show a very similar clinical picture consisting of hypertension, renal failure, and hypertensive retinitis with papilledema." He adds, "The separation of the various entities is most easily achieved by careful observation of the natural history of their development." It seems probable that the latter statement is particularly true with respect to the differentiation of the retinal pictures characteristic of these different entities.

It was essentially from this viewpoint that I stated in 1935: "In acute glomerulonephritis, as ordinarily seen, retinal changes are not found. Perhaps in most cases, mild retinitis develops at the onset and is characterized by mild hyperemia or ischemia of the disk, some arteriolar constriction, mild edema of the retina and a few flame-shaped hemorrhages in the vicinity of the disk (acute angiospastic retinitis). This retinitis, however, may last only a few days and may leave only slight residuals; thus the majority of patients with acute nephritis will show normal fundi. The fundi remain normal until the terminal stage of the nephritis is heralded, from the ocular standpoint, by the usually sudden appearance of retinitis. During the quiescent period, no changes in the arterioles are visible by means of the ophthalmoscope. The retinitis then develops without preceding arteriolosclerosis and is distinguished by this fact from the retinitis of primary hypertensive disease." Obviously, not all cases of glomerulonephritis run this course, through an acute, a latent, and a terminal period, and the variability of the course in individual cases accounts for much of the variability of the retinal lesions in any particular group of cases. In recognition of this fact, I stated also: "In cases in which there is persistent hypertension with associated retinal arteriolosclerosis following acute nephritis, the residual lesion seems to be generalized progressive vascular disease rather than typical chronic glomerulonephritis; the retinitis which then develops will be of hypertensive rather than nephritic type. When the subject in such a case comes to necropsy, the kidneys present the picture of arteriolosclerosis rather than of terminal glomerulonephritis. Retinal arteriolosclerosis is never an indication of nephritis but only of the diffuse vascular disease which complicates the nephritis." A very similar line of thought was expressed by Friedenwald, also in 1935, when he stated that in retinitis of nephritis, of toxemia of pregnancy, and of malignant hypertension, "there is no essential difference between the retinal lesions which form the picture of albuminuric retinitis."

In essential hypertension "which slowly turns into the malignant form," "the appearance of the retinitis is often sufficiently delayed to allow the development of marked, ophthalmoscopically visible changes in the medium and large-sized retinal vessels prior to the retinitis." Cases of toxemia of pregnancy and of malignant or fulminating nephritis may run their whole course in a few weeks or months and "there is at the outset no ophthalmoscopic evidence of disease of the retinal vessels antecedent to the retinitis."

In the type of acute glomerulonephritis which occurred during the war of 1914–1918 and which was known as "trench nephritis," the ocular fundi were said to show initially slight peripapillary edema and a few hemorrhages in the retina accompanied probably by generalized constriction of the arterioles. These lesions were usually transient and could be attributed either to the general toxic state or, more probably, as suggested by similar changes seen in the ordinary types of acute glomerulonephritis, to the initial rise of blood pressure. Fishberg and Oppenheimer reported 27 cases of "acute and subacute" glomerulonephritis in which the disease was of less than 5 months duration. Hypertension was present in 21 of the 27. In 1 patient there was a malignant hypertensive neuroretinitis. This patient died in 2 months. In 1 case there were choked disks and in 8 cases haziness of the optic disks or constriction of the arteries or both. Fishberg and Oppenheimer stated: "The small incidence of severe retinal lesions in acute glomerulonephritis is probably correlated with the fact that hypertension, the pathogenic factor underlying the retinal lesions, is marked and persistent in only a small part of the cases, though present at one time or another in the large majority of instances. Slight changes notably narrowing of the arteries or haziness of the disk, are found in a considerable proportion of the cases, particularly if the fundus is examined repeatedly. They have no especial prognostic significance. The same is true of the occasional small hemorrhages that are found in the fundi; they may be present in the absence of notable hypertension and are apparently akin to the purpuric spots in the skin that are not uncommon in acute glomerulonephritis." Elwyn states that, in acute diffuse glomerulonephritis, "In the retina the contraction of the arteries is shown by their narrowing, and with it are the signs of acute arteriospastic retinitis, edema, cotton-wool patches and hemorrhages." In his series of 31 cases of acute glomerulonephritis, Gresser stated that only 1 showed retinopathy, which was mild and developed 1 day before death in uremia. It is rather difficult, however, to interpret the other figures given by Gresser in reference to his cases, since he states that 22.5% (7 cases) showed edema of the disk or retina, and that 4 had "hypertensive" and 5 "sclerotic" changes in the retinal vessels. These latter changes could hardly have been due to the nephritis, since the average duration of the disease was given as 2.8 weeks. In the main, as stated by Duke-Elder, "it is generally agreed that in the first attack of acute glomerulonephritis retinopathy does not occur." Therefore, the remainder of this review will deal entirely with chronic glomerulonephritis.

Pathogenesis. It is quite generally agreed that the vascular lesions in the retina, generalized and localized constriction of the arterioles and arteriolosclerosis, are directly related to hypertension. Clinically, it seems to be rather definitely established that elevation of blood pressure precedes arteriolosclerosis and is the direct cause of its development. As stated by Ellis, the arteriolar lesion is a direct result of the hypertension, and renal arteriolosclerosis is the result and not the cause of the hyper-

tension. Studies on the hypertension produced in experimental animals by renal ischemia support this view of the development of arteriolosclerosis. Whether constriction of the arterioles precedes or follows the development of hypertension is not so clear, but it is perhaps more logical to assume, with Mosenthal, that peripheral vasoconstriction is secondary to the elevation of the blood pressure.

It is difficult to establish a single or unitarian mechanism for the development of the retinopathy, or rather retinopathies, that occur in glomerulonephritis. "Toxemia" and "arteriosclerosis" have battled back and forth through the years. The conception that retinitis in "nephritis" is due to a disturbance in circulation, to which modern thought may be said to have returned, was advanced first by Traube in 1871. He suggested a secondary increase in tension in the aortic system. In 1863, von Graefe and Schweigger "ascribed the retinal lesions to a generalized disease of the vascular system (arterio-phlebo-sclerosis) which affected the kidney as well" (Duke-Elder), although they had stated in 1860 that the retinitis was due to the toxic action of nitrogenous waste products in the blood. The opinion that the retinopathy was due to local sclerosis in the arteries of the retina was supported especially by Duke Carl of Bavaria (1887) and by von Michel (1899) and in the arteries of the choroid by Cohen (1922). Demonstration by histologic as well as clinical investigations that retinopathy can be present without local arteriosclerosis was furnished by Treitel (1876), Opin and Rochon-Duvigneaud (1903–1904) and Schieck (1907). This led to the more widespread acceptance of the theory that the retinopathy was due to "azotemia" as claimed especially by Rochon-Duvigneaud (1904), Leber (1909), and Widal, Morax and Weill (1910). The theories of increased toxic polypeptides in the blood (Dejean, 1932) and of hypercholesterinemia (Chauffard, 1912) have received less general credence. Clinically, it is difficult to substantiate any of these theories, since it is known that retinopathy is absent in many cases where the values for these substances in the blood are quite high and is present in many instances where the values are normal or low. Verwey in 1927 and Kyrieleis in 1930 were able to demonstrate by fat stains in frozen sections of the retina hyaline lipoid degeneration of the walls of the small terminal arterioles. They thought that this was present in all cases of "albuminuric retinitis" and that it was the cause of the lesions in the retina. In the meantime, however, Volhard in 1929 had stated his thesis that increase in blood pressure in itself was the cause of the retinal lesions. He thought that spastic contraction of the arteries resulted in local ischemia and that the resultant anemia and anoxemia caused the ophthalmoscopically and histologically visible lesions in both the vessel walls and in the tissues of the retina. He introduced the term "angiospastic retinitis." Friedenwald confirmed the findings of Verwey and Kyrieleis and expressed his conviction that "albuminuric retinitis is in essence a complication of retinal arteriolar sclerosis." He was willing to accept Volhard's concept of arteriolar spasm but was not willing to accept his conclusion that the arteriolar and the retinal lesions are essentially coincident results of ischemia, since he believed that arteriolar sclerosis and necrosis preceded the development of the retinal lesions proper. He theorized that Volhard's vasopressor substance might be toxic and might directly produce the hyaline degeneration of the smaller vessels, or that transient arteriolar spasm might cause sufficient anoxemia in the tissues of the retina to result in the formation of a trypsin-like substance which could cause the arteriolar lesions. Retinopathy would then occur

as a sequence to the arteriolosclerosis. He called attention to the frequent occurrence of retinal arteriolar sclerosis in chronic glomerulonephritis even when there are no arteriolar lesions in the kidneys or in any other organ. It is well to note, however, that Friedenwald refers to the hyaline lipoid degeneration of the terminal arterioles and not to changes in the main branches of the central artery of the retina.

Whatever the exact local mechanism of the development of the retinopathy may be or, as Friedenwald puts it, whatever is "the correct way in which to arrange the progressive order of arterial spasm, arteriolar sclerosis, and retinitis," most authors are now agreed on the close association between hypertension and retinopathy in the various forms of nephritis. The series of cases reported by Fishberg and Oppenheimer, by O'Hare and Cannady, and by Graham, all demonstrate this fact. More recently, Fishberg stated again: "The incidence of retinal lesions in any renal disease strictly parallels the elevation of the blood pressure; moreover, it parallels the elevation of the diastolic, and not the systolic pressure." In a recent discursive article, Elwyn advances his idea of the pathologic physiologic mechanism by which hypertension causes retinopathy. He regards as the common factor in the pathogenesis of the edema, cotton-wool patches, hemorrhages and deposits of hyalin and lipids in any of the vascular retinopathies, the dilatation of the precapillary arterioles, the capillaries and the postcapillary venules consequent to contraction of the small arteries. The resultant slowing of the circulation causes a diminution in the oxygen supply which in turn brings about a softening and increased permeability of the capillary wall. When the arterial contraction is of rapid onset and rather short duration an "acute arteriospastic" retinopathy develops which clears up after relaxation of the contraction. "When the arterial contraction persists for a sufficient time, the retinal tissue remains in a state of chronic deficiency of oxygen. . . . . The deposits of hyalin and lipids and the star-shaped figure in the macular area are the result of the deficiency in the supply of oxygen . . . . chronic arteriospastic retinitis, or retinopathy."

In the main the histologic changes visible in the retina and choroid do not aid in differentiating the retinopathy occurring in chronic glomerulonephritis from that met with in cases of primary hypertension or in establishing the pathogenesis of the retinopathy. The essential morphologic features of these retinopathies are listed by Friedenwald as: edema of the retina and optic disk; serous, fibrinous, hemorrhagic extravasations in the retina; cytoid bodies in the nerve fiber layer; flat serous detachment of the retina; arteriolar occlusion and retinal infarction, and secondary and reparative processes, including lipoid, especially cholesterol, deposits about the retinal lesion, fat droplet cells, scarring of the retina and glial proliferation, and cystic degeneration. However, Koyanagi adds to these what he considers to be the most characteristic feature of the retinopathy, a lesion of the pigment epithelium of the retina in which the cells become swollen, secrete an excess amount of fluid which accumulates under and infiltrates the retina, and take on active phagocytic properties. Koyanagi does not think that this lesion can be produced by ischemia alone and believes that its presence proves the important part played by some toxic substance in the pathogenesis of the retinopathy. As Duke-Elder sums it up: "It seems of unusual significance that the two most common features in all renal retinopathies are hypertension and attenuated arteries. . . . . Most pathologists, however, would not agree that all the changes are the result of a simple ischemia, and would prefer to assume the presence

of two factors—(1) hypertension with ischemia and subsequent malnutrition together with (2) the effect of some toxin or toxins unknown."

It is unquestionably true that in certain cases of chronic glomerulonephritis it is difficult or impossible to substantiate ophthalmoscopically the assumption that hypertension and arterial or arteriolar constriction are responsible for the lesions seen in the retina. In 1939, Lagrange called attention to the part played by the toxic or "azotemic" anemia of chronic glomerulonephritis in the production of the retinal changes. It was with reference to these cases that I said in 1935: "In most cases of chronic glomerulonephritis the retinitis is of the edematous or vascular type just described. In some cases, however, from the standpoint of the retina, the secondary anemia associated with the renal insufficiency seems to be the dominant factor. In such cases mild retinitis will be seen, hardly distinguishable from that found in pernicious anemia or in anemia secondary to carcinomatosis. The disk is definitely anemic, and scattered superficial cotton-wool patches and hemorrhages, usually of the irregularly round type with white centers, characteristic of anemia are found in a slightly edematous retina. . . . . Retinitis of this type is seen only in cases in which the secondary anemia is severe and in which the concentration of hemoglobin is less than 40% (Dare). It is not clear why this retinitis develops in place of the typical retinitis of nephritis."

Nomenclature and Clinical Features of the Retinopathy. Among the earlier authors, all of the retinal lesions occurring in any form of "chronic nephritis" were designated "albuminuric retinitis." When the distinction between primary or essential hypertension and primary nephritis began to be recognized, the terms retinitis of nephritis or renal retinitis or retinopathy came into vogue for the designation of the retinal lesions of primary nephritis. More recently, names such as "angiospastic" or "ischemic" or "hypertensive" retinitis or retinopathy have been more in favor as indicating the fundamental underlying factor in the production of the retinal lesions. Because of the considerable variation in the retinal pictures presented by individuals in any group of patients with chronic glomerulonephritis, attempts have been made recently by several authors to divide the "retinitis of nephritis" into subgroups, each of which has a somewhat different diagnostic and prognostic significance and perhaps a different pathogenesis.

Fishberg speaks of the occurrence in chronic glomerulonephritis of arteriosclerotic retinopathy and malignant hypertensive retinopathy. By "arteriosclerotic retinopathy" he means hemorrhages and "white spots" due to arteriosclerosis of the retinal arteries. He differentiates this from malignant hypertensive retinopathy by the absence of papilledema and of cotton-wool patches. In "malignant hypertensive retinopathy" papilledema and cotton-wool patches are frequent in addition to the "hard" white spots. "The arterial blood columns are narrowed generally to a striking and sometimes to an extreme degree." "Arteriosclerosis of the retinal arteries may or may not accompany this form of retinal lesion. In long-standing cases of essential hypertension or chronic glomerulonephritis, evidences of arteriosclerosis are generally present and may be marked." "In instances in which the hypertension is of brief duration, arteriosclerosis is absent." Of "arteriosclerotic retinopathy," Fishberg says: "When well-marked, it is found only where hypertension has existed for a considerable time. . . . . The large majority of cases in which the picture occurs are those of essential hypertension. But we have also

seen a considerable number of examples in glomerulonephritis of many years' duration."

O'Hare and Cannady adopted the classification of Fishberg, except that they substituted the term "hypertensive neuroretinopathy" for malignant hypertensive retinopathy. However, in 5 of their patients, they stated that the lesions in the retina progressed from hypertensive retinopathy into a late stage of arteriosclerotic retinopathy and that, in their opinion, these retinopathies were only variations or stages of the same pathologic process. They stated also that there was "no distinctive type of retinal lesion accompanying chronic glomerulonephritis." All but 2 of their 25 patients who eventually developed advanced retinopathy passed through the stage of uncomplicated arteriolar sclerosis, and O'Hare and Cannady believed that the retinal lesions were secondary to primary vascular disease.

Gresser does not use any very definite classification into types of retinopathy but seems to favor descriptions of the ophthalmoscopically visible lesions on the basis of "hypertensive" and "sclerotic" changes in the vessels and "secondary retinal phenomena." This method of recording individual lesions instead of using an inclusive name, if universally employed, would certainly be of more value in estimating the nature and degree of the pathologic processes in any particular case and might ultimately lead to a more uniform interpretation of the abnormal findings. Admittedly, it is more difficult and more subject to misinterpretation in the hands of inexperienced observers than is a general picture diagnosis. For names, Gresser favors "hypertensive retinopathy" and "hypertensive neuroretinopathy."

For designating the retinopathies seen in patients with chronic glomerulonephritis, Graham uses the terms "retinitis of anemia" and "acute angiospastic retinitis." He subdivides the latter into "acute angiospastic retinitis without chronic sclerosis of retinal arterioles" and "acute angiospastic retinitis with chronic sclerosis of retinal arterioles." With the assumption that "acute angiospastic retinitis" includes edema of the retina with or without edema of the optic disks, hemorrhages, cotton-wool patches, and edema residues such as macular stars and the like, the above classification is self-explanatory. The group "acute angiospastic retinitis with chronic sclerosis of retinal arterioles" can be further subdivided, if desired, according to the classification of Keith into "retinitis of diffuse arteriolar disease with hypertension group 3" (without papilledema) and "retinitis of diffuse arteriolar disease with hypertension group 4" (with papilledema—"retinitis of malignant hypertension"). This classification is rather heavy and cumbersome, but it does seem to make possible the presentation of the fundamental characteristics of the retinal lesions in any given case. Under the "retinitis of anemia," Graham included cases with normal retinal vessels and a few cotton-wool patches or hemorrhages in the retina, similar to those seen in cases of severe anemia of non-nephritic origin.

In his discussion of "Arterial Hypertension," Elwyn introduces the terms "acute arteriospastic retinitis" and "chronic arteriospastic retinitis." He states that in the chronic form of diffuse glomerulonephritis, "all possible combinations of the signs of acute and chronic arteriospastic retinitis may be seen in the course of the disease. With the passing of years the signs of aging and of sclerosis of the retinal vessels are added. In the advanced stage of the disease, with high blood pressure, renal insufficiency

and the full-blown picture of acute and chronic spastic retinitis, differentiation between this disease and the malignant stage of essential hypertension may be difficult."

Offhand, there would appear to be little in common between the views of these various authors. But, on closer inspection, it is evident that through the reports of Fishberg, O'Hare and Cannady, Gresser, and Graham, there runs a certain thread of similarity and agreement in spite of the different modes of expression. It becomes obvious that, in the minds of all, the retinopathy usually seen in association with chronic glomerulonephritis is in essence "hypertensive" or "angiospastic" or "ischemic" or "anoxemic" or "arteriosclerotic," which basically are all the same—nutritional; that this retinopathy can occur in the absence of clinical arterial or arteriolar sclerosis and that when arteriolosclerosis is seen in the retina it indicates that diffuse arteriolosclerosis is complicating the glomerulonephritis. Thus, Graham stated that in the 8 patients in his group who showed chronic sclerosis in the retinal arterioles, arteriolosclerosis was found in the kidneys and also in other organs which were examined: heart, liver, pancreas and brain. And Fishberg stated, "In the cases (of retinal arteriolosclerosis or arteriosclerotic retinopathy) that came to necropsy the glomerulonephritis was accompanied by arteriolosclerosis and usually by marked general arteriosclerosis; as is the case in essential hypertension, the retinal arteriosclerosis is but one manifestation of injury to the arteries, and particularly of the arterioles, wrought by long-standing hypertension."

Incidence and Clinical Significance of Retinopathy. It is interesting to compare the incidence of retinal lesions in the groups of cases of chronic glomerulonephritis reported by Fishberg and Oppenheimer, O'Hare and Cannady, Gresser, and Graham. In Fishberg and Oppenheimer's series there were 55 cases, 19 of which died under observation. Of the entire group, 41.8% had retinopathy; 73.7% of the cases that died had retinopathy. In O'Hare and Cannady's series there were 32 cases, all with normal ocular fundi or only minimal retinal arteriolar sclerosis at the time of the initial examination, examined repeatedly over an average period of 4 years, and 21 followed until the time of death. Of this group, 78.1% had retinopathy. In Gresser's series there were 50 cases. The number that died under observation is not stated. Of this group, 56% had retinopathy. In Graham's Series 1, there were 56 cases; all died under observation and the diagnosis of chronic glomerulonephritis was confirmed at necropsy. Of this group 82.1% had retinopathy. In Graham's Series 2, there were 50 cases, none of whom died under observation. Of this group, 34% had retinopathy. If the 2 series of Graham are combined, a total of 106 cases, 59.4% had retinopathy. From a comparison of these statistics, it is apparent that retinopathy is a relatively terminal event in chronic glomerulonephritis. Thus, it will be noted that in Graham's Series 2, in which the mortality rate under observation was 0, the incidence of retinopathy was 34%. In Fishberg and Oppenheimer's series, in which the mortality rate was 34.5%, the incidence of retinopathy was 41.8%. In O'Hare and Cannady's series, in which the mortality rate was 65.6%, the incidence of retinopathy was 78.1%. And, in Graham's Series 1, in which the mortality rate was 100%, the incidence of retinopathy was 82.1%. The relatively late development of retinopathy in chronic glomerulonephritis as compared to primary hypertensive disease is probably due to the fact, as noted by Wilson, that "in chronic nephritis severe hypertension is usually a late feature."

XUM

Of the 23 cases of retinopathy in Fishberg and Oppenheimer's series, 6 were arteriosclerotic and 17 were hypertensive in type; in O'Hare and Cannady's series, 11 of 25 were arteriosclerotic and 14 were hypertensive; in Graham's combined series, 11 of 63 were anemic and 52 angiospastic or hypertensive in type. Thus, of a total of 111 cases of retinopathy, 83, or 74.7%, were of the hypertensive type. This is further evidence that, in glomerulonephritis, hypertension is the predominant factor in the production of the retinopathy. Since, among the 39 cases of angiospastic retinopathy occurring in his group of necropsy-proven cases, only 8, or 20%, showed definite ophthalmoscopic evidence of arteriolosclerosis, Graham considered "acute angiospastic retinitis without chronic sclerosis of the retinal arterioles" to be the most characteristic retinal lesion in chronic glomerulonephritis.

The question of the occurrence or incidence of sclerosis of the retinal arterioles in chronic glomerulonephritis is one of considerable interest. Eight (14.6%) of Fishberg and Oppenheimer's 55 cases showed uncomplicated retinal arteriolosclerosis as did 5 (15.6%) of O'Hare and Cannady's 32 cases, and 16 (15.1%) of the 106 cases in Graham's combined series. This is a remarkably close agreement by different observers and might well be considered to represent the expected incidence of retinal arteriolosclerosis among cases of chronic glomerulonephritis. The possibility that this figure (approximately 15%) is correct is supported further by the fact that in Graham's Series 1 (necropsy-proven cases) the total incidence of retinal arteriolosclerosis was 14.2% (8 of 56 cases). In all of these cases, retinopathy was present also, which would suggest that all patients who have both diffuse arteriolar disease and glomerulonephritis will develop retinopathy before death. The higher total incidence of retinal arteriolosclerosis in the series of Fishberg and Oppenheimer (no definite figure given) and of O'Hare and Cannady (87.5%) may possibly be explained by the inclusion of angiospastic lesions with the sclerotic lesions of the arterioles. This still leaves unexplained the apparent higher total incidence of retinal arteriolosclerosis in Graham's Series 2 (40%) than in Graham's Series 1 (14.2%). The explanation suggested by Graham, that some of the cases that did not come to necropsy might really have been cases of primary hypertensive disease, is worthy of consideration. However, an alternative explanation may be that the cases of chronic glomerulonephritis in which chronic hypertension and arteriolosclerosis became the outstanding feature rather than progressive renal insufficiency run a longer course and are less likely to reach their terminal phase during a relatively short period of observation. The possibility that the latter explanation may be the correct one is supported somewhat by the fact that the average length of life after the probable onset of the retinopathy in Graham's cases was definitely longer in the group with arteriolosclerosis than in the group without arteriolosclerosis (6.2 months as compared to 4 months).

It is the general impression that all patients with chronic glomerulonephritis will develop retinopathy before death. So that there is a tendency to rule out the diagnosis of chronic glomerulonephritis in a moribund patient if the ocular fundi are normal. However, in Graham's Series 1, the fundi were normal 2 weeks before death in 4 patients, 1 week before death in 2, and 2 days before death in 4. This would suggest the possibility that the fundi may be normal even in the terminal stages in about 20% of patients dying from chronic glomerulonephritis, and consequently that uremia may be due to chronic glomerulonephritis even if no lesions are visible in the

retina. This fact is pointed out also by Fishberg and Oppenheimer. Four of their 18 patients who died in uremia had normal fundi (22%).

The serious prognostic significance of "albuminuric retinitis" was recognized essentially from the time of its establishment as an entity. Since the separation has been made between chronic glomerulonephritis and essential and malignant hypertension, it has become obvious that life expectancy after the development of retinopathy is even shorter in cases of glomerulonephritis than in cases of malignant hypertension. Thus, Graham found that the mean duration of life after retinopathy developed was 4.3 months in chronic glomerulonephritis as compared to 13 months in malignant hypertension. And O'Hare and Cannady gave the average life expectancy as 6.3 months, with 23 months as the longest duration of life of any patient with retinopathy in their series.

Assuming that a rather rapid rise of the blood pressure above its previous levels is the main factor in the development of the retinopathy, then the reason for the serious prognostic significance of the retinopathy becomes apparent. For, as Wilson states, "It is a common observation that in chronic nephritis, once the blood pressure rises over 200 mm., the patient's condition deteriorates by what may be termed 'geometrical' progression." It is true, however, that an occasional patient with chronic glomerulonephritis will pass successfully through an acute angiospastic episode with retinopathy. The blood pressure will fall, the retinopathy recede, and the patient may remain in relatively good condition for a considerable period of time.

In a study of the "vascular phase" of chronic diffuse glomerulonephritis Horn, Klemperer and Steinberg (*Arch. Int. Med.*, **70**, 260, 1942) classified 49 cases into "slowly progressive," "transitional accelerated" and "advanced accelerated" groups on the basis of the type of arteriosclerosis present in the kidneys at necropsy. They stated that narrowing and irregularity in caliber of the retinal arterioles, arteriovenous compression and exudates in the retina were present in all groups. However, the optic discs were normal in all cases of the "slowly progressive" group; while papilledema was present in 62 per cent of the "transitional accelerated" and in 96 per cent of the "advanced accelerated" cases. "It appeared in this study that when severe hypertension had become definitely established, advanced neuroretinopathy either was coëxistent or was soon to follow, and further, that it indicated the probable existence of accelerated visceral vascular lesions."

These authors do not think that the lesions in the retina in chronic glomerulonephritis differ in any essential way from those seen in other forms of hypertensive disease. They state: "It is worthy of reëmphasis that the neuroretinopathy of hypertensive patients is in no way induced by the azotemia but is rather the expression of an increased intracranial pressure or is incident to the occurrence of ocular vascular lesions and should be viewed as evidence of the accelerated or malignant phase of hypertension no matter what its basic cause may be. It appears more accurate then, to refer to the full development of this clinical picture in which severe hypertension and papilledema exist as the syndrome of 'malignant hypertension,' possibly associated with accelerated arteriosclerosis, and the presence of all disease entities which are capable of producing this clinical picture should be duly suspected." They think that the height of the blood pressure and the presence of neuroretinopathy are the cardinal clinical criteria for the recognition of the accelerated phase of the arterial complications of chronic glomerulonephritis.

Comment. It is apparent from a review such as this that considerable uniformity is being attained in the interpretation of some of the fundamental factors in cardiovascular renal disease and its complications in the retina. It is obvious, however, that there is a great need for the establishment of a more uniform nomenclature of and for more uniform criteria for the diagnosis of vascular disease in the retina.

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PHYSIOLOGY

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Electrical Activity of Acetylcholine at Phase Boundary Between Cholesterol and Saline. R. BEUTNER and T. CUNLIFFE BARNES* (Hahnemann Medical College of Philadelphia, Departments of Pharmacology and Physiology). Negative electrical potentials arise through contact of cholesterol or lecithin (dissolved in benzyl alcohol) with acetylcholine and also sympathetic amines.

Benzyl alcohol without addition of a lipoid gives *no* potential with acetylcholine. Unmodified benzyl alcohol gives some potential with the sympathomimetic amines but weaker than if lipoid is added to the benzyl alcohol.

These results were obtained with our "oil" cell technique. The decisive experiments are: (1) Pure benzyl alcohol is filled into the "cup" of our "oil" cell. The beaker holding this cup is first filled with saline; acetylcholine added, even as much as 2% (a relatively high concentration), produces *no* change in the electromotive force. (2) When *0.6% cholesterol*

* The writers wish to express their appreciation to Miss Carol E. Erickson and Mr. Clifford Gilbert for their technical help in this work.

is added to the *benzyl alcohol* in the oil cup an electric negativity appears when acetylcholine is added to the saline solution in the beaker, as the following figures show:

ADDED TO THE AQUEOUS SALINE IN BEAKER	ELECTRIC NEGATIVITY
0.05% acetylcholine	6.0 millivolts
0.10% "	10.0 "
0.15% "	14.0 "

(3) Concerning the action of the sympathomimetic amines we used paredrine HCl and benzedrine HCl instead of the unstable epinephrine. Benzyl alcohol without addition gave a potential of 4 mv. when 0.05% paredrine was added to the salt solution. However, benzyl alcohol plus 0.6% cholesterol gave a slightly greater value, *viz.*, 13 mv. Thirty per cent lanolin in benzyl alcohol gave 12 mv. Also tricaproin gave 26 mv. with benzedrine, but no potential at all with 0.05 to 1% acetylcholine. This finding suggests that glycerides are preferably contained in the "adrenergic" fibers being responsible for their response to sympathin.

The Importance of Insensible Water Loss in the Metabolism of the Rat. DAVID M. TENNENT (Merck Institute for Therapeutic Research, Rahway, N. J.). A method is described for the separate determination of the insensible water loss from the skin and from the lungs of individual rats. Three groups of experiments were performed with 5 rats in each group. The rats of the first 2 groups were anesthetized with nembutal or urethane, and the experiments were run at 50% relative humidity and 2 temperature levels. For the first group, at 23° C., the average water loss from the skin was 72% of the total evaporative loss, and for the second group, at 34° C., 73%. The group at 23° suffered a loss of body temperature and had a total water loss which was only one-half that of the group at 34°.

The third group of experiments was performed on non-anesthetized rats at 24° C. The total evaporative loss was the same as that from anesthetized rats that suffered no drop in body temperature, but only 57% of the water came from the skin. This is approximately the same as the amount from human subjects who are not actively sweating. The water loss from the skin of the rat is probably a process of diffusion and evaporation rather than of secretion.

The respiratory volume and the peripheral blood flow, which are under the control of the rat, are more important than environmental factors in determining the insensible water loss. The loss from fed rats is greater than from fasting rats, and the loss is more rapid at night than during the day. Rats at 90° F. and 90% relative humidity lose as much as rats at 74° F. and 50% relative humidity, in spite of the fact that their spontaneous activity is lower.

Crystallographic and Optical Properties of Human Hemoglobin. A Proposal for the Standardization of Hemoglobin.* DAVID L. DRABKIN (Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). With a view to the development of an acceptable and reliable procedure for the standardization of hemoglobin,

* Work done under contract with the Office of Scientific Research and Development.

the crystallization of the hemoglobins of different species, including man, was undertaken to secure material suitable for standardization.

Crystalline Human Hemoglobin. The preparation of crystalline human hemoglobin in a state suitable for crystallographic characterization does not appear to have been accomplished heretofore. The procedures of Green, Cohn, and Blanchard[6] and Cannan and Redish[1] yield in our hands "crystalline" refractile granules of indefinite shape. Modified procedures have been developed which yield consistently large beautiful crystals of adult human hemoglobin, upon which crystallographic information was readily obtained with the petrographic microscope. The essential step consists in securing suitable concentrated solutions of hemoglobin. Concentration is accomplished by subjecting the original stroma-free solution (obtained from the fresh corpuscles of citrated blood by thorough washing with 1.2% NaCl, containing 0.0025 M $AlCl_3$, dilution with 1 volume of water, and treatment with 2/5 volume of toluene), whose concentration in hemoglobin is of the order of 8 to 10 mM per liter (Mol. Wt. equivalent = 16,700), to dialysis in a refrigerator either against saturated $(NH_4)_2SO_4$ or against 2.8 M phosphate buffer, pH 6.8[6] until the volume of the sac contents is reduced by approximately 45%. Under these conditions 3/4 to 4/5 of the sac contents has precipitated in the form of refractile granules of oxyhemoglobin, which may be considered crystalline, but unsuitable for characterization. The supernatant solution of hemoglobin is removed. The concentration of this solution in hemoglobin is now approximately 13 to 13.5 mM per liter. Crystallization from this solution is accomplished by the cautious addition drop by drop of saturated $(NH_4)_2SO_4$ or the 2.8 M phosphate buffer.

Crystallographic and Optical Character. Identical crystals are secured whether $(NH_4)_2SO_4$ or phosphate are used. Crystallization is aided by the use of citrate or oxalate, but crystalline character is not altered by these agents, and crystallization can be accomplished in their absence. Adult human hemoglobin belongs to the *tetragonal* system, and the habit is bipyramidal, with the units in perfectly symmetrical development. The optical character is *negative*, with the characteristic uniaxial diffraction pattern and strong birefringence. The axial ratios are $a:c = 1:1.263$. Concentrated solutions prepared from the crystalline material yielded spectrophotometric constants characteristic of unaltered oxyhemoglobin. The most concentrated solution prepared was 38.2 mM per liter, or 63.8 gm. per 100 ml., pH 6.0, the highest concentration yet studied spectrophotometrically in our special 0.007 cm. cuvette.[2]

Crystalline Myoglobin. This pigment was prepared in crystalline form from horse and human cardiac muscle by slight modifications in the techniques of Theorell[8] and Morgan[7]. By slow dialysis of solutions against saturated $(NH_4)_2SO_4$ macro-size crystal clusters were obtained in the case of horse metmyoglobin. The crystals are slender *orthorhombic* prisms, with straight extinction. Crystalline human metmyoglobin was obtained for the first time; it too is probably orthorhombic.

Proposal for Standardization of Hemoglobin. By dialysis of the crystallized material against double distilled water at refrigerator temperature, salt-free solutions of hemoglobin (concentration of 4 to 6.5 mM per liter) and myoglobin were obtained. Upon such solutions the following simultaneous analyses were performed: (1) spectrophotometric determination of total pigment as cyanmethemoglobin, using the constant $\epsilon(c = 1$ mM per liter, $d = 1$ cm.$) = 11.5$ at wave-length 540 mμ, previously established on the basis of independent oxygen capacity analyses upon 15 dog bloods;[3]

(2) the photometric determination of iron;[5] (3) the determination of nitrogen. For the hemoglobin of man the respective values are: $\epsilon = 11.5$, 0.338% and 17.09%. The amount of Fe in the hemoglobins and myoglobins of man, dog, and horse is remarkably similar (average 0.339 ± 0.001 for hemoglobin, and 0.340 ± 0.002 for myoglobin). Hence, the spectrophotometric constant 11.5 for cyanmethemoglobin (a measure of total pigment) can be used interchangeably in the different species, and the determination of cyanmethemoglobin may be looked upon as equivalent to a determination of hemoglobin or hemin Fe. *Proposal 1* for the standardization of hemoglobin: Determine N upon a salt-free solution prepared as above. Prepare, upon this basis, a cyanmethemoglobin standard. Such standards can be preserved indefinitely. They have been found to undergo no change over a period of more than 6 years.

Protohemin can be prepared readily,[4] and consistently with an Fe content (average of 9 independent preparations $= 8.44 \pm 0.02\%$) of 98.5% of theory (8.57%). The spectrum of hemin dicyanide is practically identical[4] with the spectrum of cyanmethemoglobin; the millimolar (Mol. Wt. = 651) ϵ value on an Fe basis = 11.3 at 540 mμ. Hence, a hemin dicyanide solution whose concentration is based upon the amount weighed out $\times$ 1.033 (gravimetric and photometric correction factor from above data) is equivalent photometrically to a cyanmethemoglobin standard. *Proposal 2* for the standardization of hemoglobin: Weigh out a sample of crystalline hemin, dissolve volumetrically in 0.1 to 0.2 M NaOH, and convert to cyanide derivative by addition of excess solid KCN. This yields a *gravimetric standard* equivalent to cyanmethemoglobin, when adjusted as described. Aliquots of cyanmethemoglobin prepared from blood samples can be determined photometrically ("colorimetrically" with appropriate filter) against either or both of the above standards, and may thus be employed in the calibration of any procedure for the quantitation of total hemoglobin.

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The Nature of Intercalated Disks of Cardiac Muscle Studied by the Microdissection Method. GEORGE S. DE RENYI (Department of Anatomy, University of Pennsylvania). Pieces of cardiac muscle tissue obtained from various species of mammals were studied in properly balanced physiologic solutions. Intercalated disks were found in fibers responding with contraction to mechanical stimulation. The number, appearance and distribution of this structure in suddenly killed animals has shown no divergence from those in the tissues obtained from other animals dying more slowly. Six hours after death the disks appeared in the same fashion as in the freshly killed animals. The intercalated disks showed resistance to pull, whether it was applied in longitudinal or in transverse direction. It is evident that the substance at the disks is harder than in between. When saline was injected under low pressure into the fiber the

disk prevented the trespass of the liquid from the injected segment to the succeeding one. But the disk broke to parts when the pressure was increased and the saline flowed over into the next segment.

In the course of these studies it became evident that the substance at the disks is considerably harder than the sarcoplasma proper. There was no indication, however, of the existence of a cell membrane at the level of the disk. Conclusion was drawn that the myocardium is a large plasmodium, probably a single multinucleated cell. It is segmented, softer and harder parts alternating, but no cell membranes exist crossing the fibers at any location.

BOOK REVIEWS AND NOTICES

THE METHODOLOGY OF PIERRE DUHEM. By ARMAND LOWINGER. Pp. 184. New York: Columbia Univ. Press, 1941. Price, $2.25.

THE philosophic attitudes of great scientists, especially those who live near the end of an era in scientific thought, are a necessary part of the "evidence" on the basis of which the philosopher of science constructs his theory of experimental method. The scientific mind at the end of an era seems to be more self-conscious of the purposes of science, more reflective upon them, than the mind that finds itself in the midst of a process whose end-point is not at all clear and whose success does not seem to be at all assured.

If this much be so, then the philosopher of science would do well to pay special regard to the writings of Pierre Duhem. He is a genius of a scientific age that had grown optimistic indeed regarding the future of science. Closely analogous to the rationalistic optimism of the seventeenth century concerning the hope of remodeling all science in the framework of the *scientia perfecta*, geometry, was the nineteenth century's optimism towards the future of physics based on the model of the classical mechanics. The attitude, to be sure, was more dynamic in its willingness to admit that basic changes in physical theory might be needed, but there seemed to be no end of possibilities in this direction, and there seemed to be no barrier to the smooth-flowing progress of physical science.

This little book of Mr. Lowinger's is extremely valuable, then, for it represents practically the only complete treatment in English of Duhem's work. In a series of remarkably exhaustive but lucid chapters, Mr. Lowinger constructs the philosophic attitude of Duhem that emanated from the optimism we have described.

As might be expected, Duhem's contribution to the philosophy of theory in experimental science far outweighs what little he has to say on the philosophy of experimental "facts" or data. Indeed, the discussion of "practical" fact *vs.* "theoretical" fact (pp. 96 to 101) in Mr. Lowinger's book leaves the reader wherever he may have started; it repeats a story at least as old as Plato, that the world of sense can never have the character of precision to be found in the world of mathematics. The correspondence of the world of theory and the world of sense is difficult, and apparently the sooner we can leave the latter behind in our reflection on the processes of science, the sooner we can stand on the firm foundations that mathematical theory appears to provide. The story is as old as Plato; its answer much newer. Indeed, it was the adolescent Pragmatism of Duhem's time that was just then struggling to show that the concrete aspects of the world of sense are in reality as much theoretical constructs as are the theorems of mathematics; it was a scarcely yet formulated Experimentalism (E. A. Singer, Jr.) that proposed to consider the "practical fact," not as an immediate datum of sensation, but an ideal of experimental science as impossible to attain, and yet as approachable to attainment, as a completed mechanism.

No, if we are to reap our harvest here, its fruits are to be found in such brilliant insights into the nature of theory as are given in Chap. 8 of Mr. Lowinger's book. It requires a thorough-going formalist such as Duhem was, to see that an experiment designed to test one aspect of nature alone is no experiment at all: "the realization and the interpretation of any physical experiment whatsoever implies adhesion to a whole ensemble of theoretical propositions" (p. 140). This is a lesson that might well serve as a rebuke to some of our contemporary efforts to conduct isolated investigations independent of a general theory.

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As for Mr. Lowinger's own reflections on Duhem (Chap. 10), these appear to be born of the newer and more disturbed age in physical theory; far from the optimism of a Poincaré, asserting that the scientist has an "infinite" choice of mechanical theories, Mr. Lowinger feels that "it is with the greatest difficulty that even a single adequate theory can be arrived at" (p. 169).

What is puzzling, though, are the entire series of pronouncements of Mr. Lowinger in this final chapter. Is the author's statement, for example, that methodology is impotent to legislate for science (p. 164) to be taken to mean that a sound statistical methodology cannot legislate the design of an experiment and the inferences therefrom? What Mr. Lowinger calls the "indefeasible facts of the scientific situation" seem to originate in a peculiar and futile attempt to maintain the autonomy of physics, even in those matters that deal with the philosophy of physics: "futile," we say, for one advances in no wise by asserting that "truth" and "reality" are out of place in physics and must be replaced by "fitness and adjustment to the actual scientific process." The meaning of this last phrase is no easier to divine, and its divining belongs no less to a philosophy of physics, than does the meaning of truth and reality.

In a sense, this last chapter might seem to express an opposition to the feeling of calm reflection that lies in Duhem's writings. But this cannot really be the author's intent, to judge from the sympathetic and competent survey contained in the other chapters. Rather, he probably means to sound a note of caution lest the reader stray too far in his enthusiasm from the main point at issue, which is as always the progress of experimental science. C. C.

A Laboratory Manual of Physiological Chemistry. By D. Wright Wilson, Benjamin Rush Professor of Physiological Chemistry, Univ. of Penna. Pp. 269. Fifth Ed. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

Arranged as a teaching manual for laboratory techniques, this new edition of Wilson's manual is intended to be supplemented by lectures and discussions on the many topics in physiological chemistry which form the basis of understanding of so much modern medicine. There is an introductory section dealing with the chemistry of carbohydrates, fats, and proteins. The main portion of the manual concerns itself with body tissues and fluids. Considerable emphasis is placed on quantitative methods and there is a final chapter describing experiments on dietary deficiencies. W. S.

The Standardization of Volumetric Solutions. By R. B. Bradstreet, M.S. Second Ed. Pp. 151; numerous figs. and tables. New York: Chemical Publishing Co., 1944. Price, $3.75.

This book is a small manual, in which are gathered together techniques and discussions of the common volumetric methods. It is intended for the expert analyst. W. S.

Surface Chemistry. Edited by Forest Ray Moulton. Pp. 160; many figs. and tables. Washington, D. C.: Amer. Assn. for the Advancement of Science, 1943. Price, to members, $2.75; to others, $3.25.

This volume comprises a symposium at the University of Chicago participated in by eminent authorities in this highly specialized subject. Beginning some 50 years ago, this field has expanded until now it occupies the full time of many investigators throughout the world. Difficult techniques and detailed theories have been elaborated which form the basis for the understanding of important biologic phenomena. This volume is a survey of current aspects of a difficult field. W. S.

PRACTICAL METHODS IN BIOCHEMISTRY. By FREDERICK C. KOCH, Frank P. Hixon Distinguished Service Professor Emeritus of Biochemistry, Univ. of Chicago; Director of Biochemical Research, Armour & Co., Chicago, and MARTIN E. HANKE, Associate Professor of Biochemistry, Univ. of Chicago. Fourth Ed. Pp. 353; 20 figs.; 40 tables. Baltimore: Williams & Wilkins, 1943. Price, $2.25.

THIS manual is intended for the use of medical students. It is somewhat more than a practical laboratory aid, as it includes a considerable amount of explanatory matter on each topic covered by the experiments. Much can be said for this procedure, for it should serve to correlate more closely the student's theoretical reading with his actual laboratory practice. Some 265 experiments are described covering a very wide range of topics. Mastery of them should form an excellent background for the understanding of clinical chemistry.

W. S.

THE RADIOLOGY OF BONES AND JOINTS. By JAMES F. BRAILSFORD, M.D., PH.D., F.R.C.P., F.I.C.S. Third Ed. Pp. 440; 404 ills. Baltimore: Williams & Wilkins, 1944. Price, $12.00.

THE Third Edition of Dr. Brailsford's book follows very much the pattern established in the earlier editions of this monograph. The book is and has always been valuable because it represents, to a large extent, the analysis of the Author's experience; and in this last edition the Author has continued to bring the various cases reported up to date.

As the author stated in his first edition, this work is one in which each condition described is discussed briefly and in many instances the reviews of other authors have either been quoted or commented upon. The monograph is a valuable contribution to the radiologic literature and is used frequently by most students of radiology.

The paper used is not as good as that used in previous editions and the publisher still uses positive Roentgen ray illustrations rather than negative. It is to be hoped that some day the excellent illustrations provided can be published as negatives, and that after the war, the paper also will be more satisfactory.

E. P.

ATLAS OF THE BLOOD IN CHILDREN. By KENNETH D. BLACKFAN, M.D., Late Thomas Morgan Rotch Professor of Pediatrics, Harvard Med. School; Late Physician-in-Chief, Infants' and Children's Hosps., Boston; LOUIS K. DIAMOND, M.D., Assistant Professor of Pediatrics, Harvard Med. School; Visiting Physician and Hematologist, Infants' and Children's Hosps., Boston. With illustrations by C. MERRILL LEISTER, M.D., Associate Pediatrician, St. Luke's Hosp., Bethlehem, and Allentown Gen. Hosp., Allentown, Pa. Pp. 320; 70 ills. in color. New York: Commonwealth Fund, 1944. Price, $12.00.

WE know of no atlas of the blood in children which will compare with this authoritative and beautifully illustrated volume; and in no medical books are illustrations more important than in a hematological atlas. By the use of high magnifications—mostly well over 1000—the artist, himself a pediatrician, has been able to portray many nuclear and cytoplasmic details without loss of verisimilitude. Opposite each of the 70 polychrome plates is an outline drawing of its cells, each numbered when appropriate, together with a key to facilitate identification, and other notes. The text, which occupies a full first half of the volume, gives "brief descriptions and discussions of various disease entities, including causes, symptoms, morphological variations in the blood, and treatment, with illuminating case histories."

In the consideration of such an excellent work as this, we hope that it will not appear captious to express regret that the text did not go two steps further: (1) to include even a brief consideration of the tissue changes as well as the "laboratory data" (*i. e.*, the peripheral blood changes) of the conditions being considered; and (2) to include in the treatise conditions other than those with

which the authors had "close personal experience." The latter, of course, carries the advantage of being built on a basis of first-hand knowledge, and one readily admits that few if any conditions of great importance appear to be missing.

The volume is the best kind of worthy memorial to Dr. Blackfan, who had planned it many years ago. As Dr. Minot points out in the Foreword, it is of value to all hematologists and internists, as much the same conditions and cells appear in adults as in children, though in different proportions and significances. We are indeed fortunate in having such a worthy volume appear at this time in spite of the necessary war-time restrictions. E. K.

CLINICAL PRACTICE IN INFECTIOUS DISEASES. For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D. (Lond.), F.R.C.P., D.P.H., and M. MITMAN, M.D. (Lond.), M.R.C.P., D.P.H., D.M.R.E., with a Foreword by W. ALLEN DALEY, M.D. (Lond.), F.R.C.P., D.P.H. Second Ed. Pp. 570; 26 tables; 52 figs. Great Britain: Williams & Wilkins, 1944. Price, $6.00.

THIS is an ideal textbook for the medical student and practitioner. It covers all the infectious diseases, presents about each of them the facts that are of immediate practical importance and omits all theories and procedures that are now discarded. Each chapter begins with a synopsis of its contents, sufficient for a superficial review; the subdivisions of each chapter are indicated in bold type; diagnosis is clarified by illustrations, some of which are colored; tables that help in differential diagnosis are included, and at the end of each chapter is given a bibliography that renders easy access to original contributions. The first few chapters, on infection and resistance, hypersensitiveness and allergy, the transmission of infectious diseases and general clinical manifestations and diagnosis, will be found especially helpful to the student. The place of the sulphonamides in therapy is fully covered and even brief reference to penicillin is made. The newer viewpoint about infective jaundice, including postinoculation jaundice, is adequately described. The Reviewer heartily recommends this book. T. M.

A NEW GERMAN-ENGLISH PSYCHO-ANALYTICAL VOCABULARY. Research Supplements to the International Journal of Psycho-Analysis. No. 1. By ALIX STRACHEY. Published for The Institute of Psycho-Analysis. Pp. 84. Baltimore: Williams & Wilkins, 1943. Price, $2.50.

THIS small book is an excellent glossary for use by English translators and readers of German psychoanalytic literature. The German terms are well selected and their English translation is brief and satisfactorily complete. J. M.

CRIME AND THE HUMAN MIND. By DAVID ABRAHAMSEN, M.D., Department of Psychiatry, Columbia University. With a Foreword by NOLAN D. C. LEWIS, M.D., Director, New York State Psychiatric Inst. and Hosp., Columbia Univ., New York, N. Y. Pp. 244; 3 tables. New York; Columbia Univ. Press, 1944. Price, $3.00.

WITH a definitely psychoanalytic coloring, this prolific writer has discussed a timely subject in the following chapters: Criminology as a science; The mind in relation to crime; Heredity and environment as causes of crime; Functional view of the offender; Psychiatric-psychologic examination of the offender; The psychology of the individual offender: classification; Juvenile and war delinquency; The psychiatric-psychologic background of murder; The psychiatric and criminal law; Treatment and research.

Science maintains that heredity determines what we can do, while environment decides that which we do. "This means that a number of men are born to crime, that is their fate when certain constellations are fulfilled." One table gives the rise in delinquent subjects by boroughs in New York City, in the first 5 months of recent years: 1942, 2162; 1943, 2897; 1944, 3066. The more

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common juvenile crimes, larceny and burglary; 33.3 and 46.6% respectively, were committed by those under 21 years in 1941; 30 and 29.8% by those between 21 and 29. During the first half of 1941, the percentages were 34 and 48.5 of offenses by those under 21. Most adolescent crimes are petty larceny, burglary, auto theft, and statutory rape. Those of the twenties are chiefly robbery, criminal homicide, embezzlement, and fraud. Forgery is usually an offense of the more mature adult.

In 1943, a report from England told of a 41% increase in delinquency for children under 17. "In addition to this lack of supervision, living in shelters with all types of people during air raids, the blackout with its tempting opportunities for perpetrating crimes, the closing of schools, and the lack of recreational facilities all go far in instigating children to criminal activities." The fallacy of committing those with psychopathic personalities to prison is discussed, where only Federal and a few State penal institutions offer proper treatment. The possibility of homosexuality being regarded as a disease has received no such recognition in the law. In the matter of prostitution, the method employed by Denmark is commended. There, a home has been established on Sprogo Island for the mental defectives and for those on the borderline. After having been taught regular habits, the individuals are removed to places with fewer restrictions; finally, with an appropriate guardian, they are given suitable employment. It is claimed that 80% have later lived satisfactorily, and that about half actually marry.

This experienced writer has contributed a very enlightening book.

N. Y.

GYNECOLOGICAL AND OBSTETRICAL UROLOGY. By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, Johns Hopkins Univ.; Associate in Gynecology, Univ. of Maryland; Assistant Visiting Gynecologist and Gynecologist in charge of the Cystoscopic Clinic, Johns Hopkins Hosp.; Visiting Gynecologist, Church Home and Hosp., Hosp. for the Women of Maryland, and Union Memorial Hosp. Pp. 517; 220 figs. Baltimore: Williams & Wilkins, 1944. Price, $6.00.

THE Author's wide personal experience in gynecology and female urology, as head of the female cystoscopic clinic at the Johns Hopkins Hospital, qualifies him for the task of presenting a single volume treatise on urologic problems in the female. Stress is placed on the general nature of urologic disease and its relation to general medicine and the specialties, rather than on the technique of urologic surgery. However the operative techniques of several urologic procedures are presented in detail.

There are chapters on anatomy, physiology; relation of female urology to general medicine, gynecology, and obstetrics; and cystoscopic technique. The latter is entirely the Kelly method.

With this background, the author goes into the diseases of the lower urinary tract, including urethra and bladder. He next discusses incontinence of urine, retention of urine, and diversion of the urinary stream. The upper urinary tract is covered by chapters on congenital anomalies of the kidneys and ureters, ureteral obstructions, hydronephrosis, tuberculosis, non-specific infection, calculus, neoplasm, and traumatic injury.

The book is well organized and covers its intended subject adequately. Illustrations are excellent. It should be of value to medical students, gynecologists, obstetricians, surgeons, and urologists.

L. LA T.

PHYSIOLOGY IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P., Professor of Physiology and Director of Physiology Dept. in the School of Med. of Western Reserve Univ., Cleveland, Ohio. Fourth Ed. Pp. 1174; 274 figs. Philadelphia: Lea & Febiger, 1944. Price, $10.00.

FIVE years have elapsed since the appearance of the Third Edition of this well-known textbook. The presence in the Fourth Edition of 2 new chapters

on aviation physiology; 1 on hemorrhage and shock; and the increased attention devoted to such subjects as dark adaptation, camouflage, nerve regeneration, water deprivation, and so on, are a reflection of the fact that while a world war tends to check the progress of Physiology in most directions, it may accelerate it in others. By no means all of the new material has to do with war physiology, however, but is well distributed throughout the entire field. Despite some condensation in rewriting and the freer use of small type in the present volume, there has been a net increase of 30 pages in the text and an addition of approximately 1000 new references to the literature. As in past editions, the subject of the circulation is treated with especial thoroughness, and with a degree of authority possible only in the case of an author writing about a field in which he himself has made important original contributions.

M. J.

CONTROL OF PAIN IN CHILDBIRTH. By CLIFFORD B. LULL, M.D., F.A.C.S., Clinical Professor of Obstetrics, Jefferson Med. Coll.; Assistant Director, Phila. Lying-in Unit, Penna. Hospital, and ROBERT A. HINGSON, M.D., Surgeon, U. S. Public Health Service; Director, Post-graduate Medical Course, Phila. Lying-in Unit, Penna. Hospital. With an Introduction by NORRIS W. VAUX, M.D., Obstetrician-in-Chief, Phila. Lying-in Unit, Penna. Hospital. Pp. 356; 100 ills., 32 subjects in color. Philadelphia: Lippincott, 1944. Price, $7.50.

ALTHOUGH this volume considers most of the drugs and techniques which are employed for the relief of pain during labor, it deals primarily with the continuous administration of local anesthesia *via* the caudal canal. Since Hingson is the outstanding proponent of this procedure, it is important to have him publish in full the results of his own experience. This is especially true, since many obstetricians are far from being convinced that this is a practical form of anesthesia that will stand the test of time. The book deals fully with the caudal technique, but its treatment of the other drugs and methods is such that it can hardly be considered a comprehensive work of general reference. There is also much to be desired in this volume from the standpoint of authorship. These weaknesses deal with such questions as the use of source material and references, organization of the data, style, English composition, simplicity in the selection of words, as well as the most efficient use of illustrations. It is impossible in the present space to consider these points in any detail, but they are mentioned in the hope that more attention be paid to these details in a future edition.

D. M.

LARGE SCALE RORSCHACH TECHNIQUES. A Manual for the Group Rorschach and Multiple Choice Test. By M. R. HARROWER-ERICKSON, ACAD. DIP., PH.D. Research Associate Department of Neuropsychiatry, University of Wisconsin, and M. E. STEINER, B.A., M.A., Personnel Section, General Electric Co., Bridgeport, Conn. Pp. 420; 70 ills., 47 tables. Springfield: Charles C Thomas, 1944. Price, $8.50.

IT is here assumed that the Rorschach (inkblot) worker has already mastered the specialized technique. For their group administration, these authors employ large scale Rorschach techniques, thereby vastly increasing the procedure's range value. A completely new test has been devised, termed the Multiple Choice Test, made available for the screening out of maladjusted individuals. The final chapters tell how the group method combined with the Multiple Choice Test enables the "psychologist, psychiatrist, educator, social worker or probation officer, *without any Rorschach training*, to profit by the experience of Rorschach and other subsequent workers." The volume includes a scoring key employed in this test. And here is also given for the first time, a statistical analysis of the 10 Rorschach cards.

After the class has assembled for this group method, in numerical order 1 slide of all the 10 cards is shown on a screen, and from each of them every individual being tested is to make 1 choice. Previously, the members of the

class had been supplied with a large record blank containing a list of 10 subjects from which 1 is to be chosen. As an illustration, the list for Rorschach card 1 reads: An army or navy emblem, Mud and dirt, A bat, Nothing at all, Two people, A pelvis, An *X*-ray picture, Pincers of a crab, A dirty mess, Part of my body, Something other than the above. Though an untrained person may administer the Multiple Choice Test, a well trained Rorschach worker will still be required to score and evaluate the group.

The Military Psychiatric Differentiation study was conducted by Lt. Floyd O. Due, (MC), USNR, Ens. M. Erick Wright, H-V (S), USNR, and Beatrice Wright, Ph.D. After 200 neuropsychiatric cases had been explored, it was concluded that the psychoneurotic sub-groups showed the most accurate inferences of maladjustment. Many organic and convulsive states could be differentiated from other groups. Response patterns often showed the presence of a psychopathic personality. Though many mental defectives produced very abnormal response records, they were not accurately discriminatory.

At the present writing, it appears that these authors have devised a new test that will reveal, with relative accuracy, the subject's personality, together with the degree of his maladjustment. Though the tedious Rorschach procedure had already attained a large sphere of usefulness, it is a real achievement to have contributed this short-cut method. N. Y.

NEW BOOKS

Manual of Clinical Mycology. Prepared Under the Auspices of the Division of Medical Sciences of the National Research Council by NORMAN F. CONANT, PH.D., DONALD STOVER MARTIN, M.D., DAVID TILLERSON SMITH, M.D., ROGER DENIO BAKER, M.D., and JASPER LAMAR CALLAWAY, M.D. Pp. 348; 148 figs. Philadelphia and London: W. B. Saunders, 1944. Price, $3.50.

A CONCISE, correct and convenient presentation from the Duke University group of mycologists. This makes it authoritative. It is the kind of a book that has been long awaited by teachers, laboratory workers and practitioners. F. W.

Lead Poisoning. By ABRAHAM CANTAROW, M.D., Associate Professor of Medicine, Jefferson Med. Coll.; Assistant Physician, Jefferson Hosp.; Biochemist, Jefferson Hosp., Philadelphia, Pa.; and MAX TRUMPER, PH.D., Lt. Commander, H-V(S), USNR, Naval Med. Research Institute, Bethesda, Md.; Formerly Lecturer in Toxicology, Jefferson Med. Coll.; Consultant in Industrial Toxicology, Cynwyd, Pa. To the Memory of HENRY LEFFMANN, Scientist, Scholar and Philosopher. Pp. 264. Baltimore: Williams & Wilkins, 1944. Price, $3.00.

Atlas of the Blood in Children. By KENNETH D. BLACKFAN, M.D., Late Thomas Morgan Rotch Professor of Pediatrics, Harvard Med. School; Late Physician-in-Chief, Infants' and Children's Hosps., Boston; LOUIS K. DIAMOND, M.D., Assistant Professor of Pediatrics, Harvard Med. School; Visiting Physician and Hematologist, Infants' and Children's Hosps., Boston. With illustrations by C. MERRILL LEISTER, M.D., Associate Pediatrician, St. Luke's Hosp., Bethlehem, and Allentown General Hosp., Allentown, Pa. Pp. 320; 70 ills. in color. New York: Commonwealth Fund, 1944. Price, $12.00. (Reviewed on p. 273.)

Electrical Signs of Nervous Activity. By JOSEPH ERLANGER, Professor of Physiology, Washington University, and HERBERT S. GASSER, Director, The Rockefeller Institute for Med. Research. Pp. 221; 113 figs. Philadelphia: Univ. of Penna. Press, 1937. Price, $3.50.

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